00025.016100

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent 6,740,669 B1

Issued: May 25, 2004

To: Robert Portmann, Urs Christoph Hofmeier, Andreas Burkhard, Walter Scherrer, and Martin Szelagiewicz

For: CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

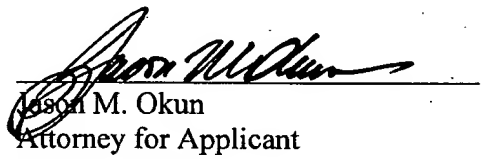
Attached in triplicate is an Application for Extension of Patent Term under 35 U.S.C. § 156 of U.S. Patent No. 6,740,669 B1.

The Commissioner is hereby authorized to charge the $1,120 fee prescribed in 37 C.F.R. § 1.20(j)(1), as well as any additional fees that may be necessitated in connection with the filing of this Application for Extension of Patent Term under 35 U.S.C. § 156, to Deposit Account No. 06-1205. Two additional copies of this transmittal letter are being submitted for charging papers.

01/13/2009 SMOHAMME 00000023 061205 6740669
01 FC:1457 1120.00 DA

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should be directed to our address given below.

Respectfully submitted,



Jason M. Okun
Attorney for Applicant
Reg. No. 48,512

Date: January 12, 2009

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

Attachs.: Three copies of Application for Extension of Patent Term under 35 U.S.C. § 156 (including Appendices A-G)
Two additional copies of this transmittal letter

00025.016100 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent 6,740,669 B1

Issued: May 25, 2004

To: Robert Portmann, Urs Christoph Hofmeier, Andreas Burkhard, Walter Scherrer, and Martin Szelagiewicz

For: CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Applicant, Novartis AG, a company organized and existing under the laws of the Swiss Confederation, represents that it is the owner of the entire title and interest in and to U.S. Patent No. 6,740,669 B1, which was granted on May 25, 2004 to Robert Portmann, Urs Christoph Hofmeier, Andreas Burkhard, Walter Scherrer, and Martin Szelagiewicz for "CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC" by virtue of the Assignment recorded on March 4, 2002 at Reel 012696, Frame 0886. Extension of the term of this patent under 35 U.S.C. § 156 is hereby respectfully requested.

By the Power of Attorney and the Statement Under 37 C.F.R. § 3.73(b), attached hereto as "Appendix A", Applicant appoints attorneys associated with Customer No. 05514 with regard to the application for the extension of the term of U.S. Patent No. 6,740,669 B1 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

I. Applicant submits this Application for Extension of Patent Term under 35 U.S.C. § 156 by providing the following information as required by 37 C.F.R. § 1.710 through 1.785, especially 1.740.

1. Identification of the Approved Product under 37 C.F.R. § 1.740(a)(1)

The complete identification of the approved product is:

chemical name: 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

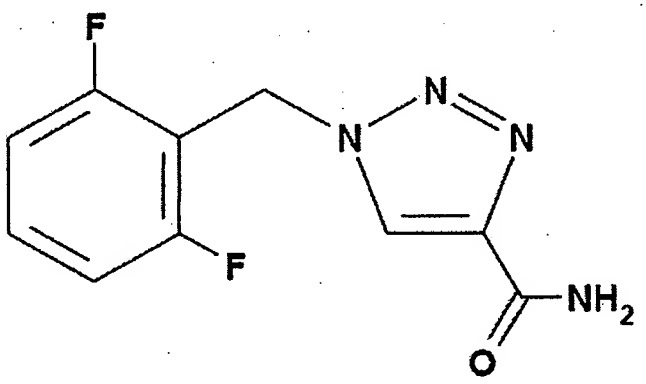
Tradename: BANZEL

generic name: rufinamide

empirical formula: $C_{10}H_8F_2N_4O$

molecular weight: 238.2

chemical structure:



A copy of the product label is attached hereto as "Appendix B".

2. Identification of the Federal Statute under which Regulatory Review Occurred under 37 C.F.R. § 1.740(a)(2)

The approved product was subject to regulatory review under the Federal Food, Drug, and Cosmetic Act, Section 505 (21 U.S.C. § 355).[1]

3. The Date of Permission for Commercial Marketing under 37 C.F.R. § 1.740(a)(3)

The approved product received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on November 14, 2008.[2] A copy of the approval letter is attached as "Appendix C".

4. Active Ingredient Statement under 37 C.F.R. § 1.740(a)(4)

The sole active ingredient in BANZEL™ is rufinamide, which has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, Section 505 (21 U.S.C. § 355) prior to the approval of NDA 21-911 by the United States Food and Drug Administration on November 14, 2008.

[1] The Investigational New Drug Application was submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. The New Drug Application was submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

[2] Applicant notes that the Investigational New Drug Application was filed by Ciba-Geigy, which merged with Sandoz in 1996 to form Novartis. The New Drug Application was filed by Eisai Co., Ltd., the exclusive licensee of U.S. Patent No. 6,740,669 B1, and its subsidiary Eisai Medical Research, Inc., in accordance with a license agreement of February 6, 2004.

5. Statement of Timely Filing under 37 C.F.R. § 1.740(a)(5)

This Application for Extension of the term of U.S. Patent No. 6,740,669 B1 under 35 U.S.C. § 156 is being submitted within the permitted 60 day period set forth in 37 C.F.R. § 1.720(f), which period expires on January 12, 2009.

6. Identification of Patent for which Extension is Sought under 37 C.F.R. § 1.740(a)(6)

The patent, the term of which this Application seeks to extend, is U.S. Patent No. 6,740,669 B1, which issued on May 25, 2004 to Robert Portmann, Urs Christoph Hofmeier, Andreas Burkhard, Walter Scherrer, and Martin Szelagiewicz. The term of U.S. Patent No. 6,740,669 B1, as calculated in accordance with 35 U.S.C. § 154, would otherwise expire on August 17, 2020 (including the 801 day extension of the original expiration date of June 8, 2018 under 35 U.S.C. § 154(b) for a delay due to appellate review by the Board of Patent Appeals and Interferences).

7. Copy of Patent under 37 C.F.R. § 1.740(a)(7)

A complete copy of U.S. Patent No. 6,740,669 B1, identified in paragraph 6 above, is attached as "Appendix D".

8. Post Issuance Activity Statement under 37 C.F.R. § 1.740(a)(8)

No Certificate of Correction, Terminal Disclaimer, Re-Examination Certificate, or Re-Issue has been issued or requested with respect to U.S. Patent No. 6,740,669 B1. The first maintenance fee for U.S. Patent No. 6,740,669 B1 in the amount of $930.00 was paid on

November 5, 2007. A copy of the Maintenance Fee Statement for the first maintenance fee is attached hereto as "Appendix E".

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product under 37 C.F.R. § 1.740(a)(9)

U.S. Patent No. 6,740,669 B1 claims the approved product. The claims of U.S. Patent No. 6,740,669 B1 cover certain crystal modifications of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, including crystal modification A, and pharmaceutical compositions that contain these crystal modifications. Claims 1-6, 9-11, and 18 read on the approved product, which contains crystal modification A.

Claim 10 reads as follows:

10. Crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide characterized by bands at 3412 cm^{-1} and 3092 cm^{-1} in the FT-IR spectrum.

Claim 10 reads on the approved product as follows:

The approved product, BANZEL™ (rufinamide), contains crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, which has bands at 3412 cm^{-1} and 3092 cm^{-1} in the FT-IR spectrum.

10. Statement of Relevant Dates to Determine the Regulatory Review Period under 37 C.F.R. § 1.740(a)(10)

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

a. An Investigational New Drug Application (IND) for BANZEL™ (rufinamide) was submitted on September 26, 1990, was received by the Department of Health and Human Services on September 27, 1990, and the IND number assigned was 35,534. A copy of the FDA letter confirming receipt of the IND is attached hereto as "Appendix F."

b. A New Drug Application (NDA) was received by the Department of Health and Human Services on November 17, 2005 and the NDA number assigned was 21-911.

c. The date on which NDA 21-911 was approved is November 14, 2008.

11. Brief Description of Activities Undertaken During the Regulatory Review Period under 37 C.F.R. § 1.740(a)(11)

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as "Appendix G" is a chronology including all major communications between the U.S. Food and Drug Administration and the Applicant in connection with the IND and NDA during the periods mentioned in paragraph 10 above.

12. Opinion of Eligibility for Extension under 37 C.F.R. § 1.740(a)(12)

Applicant is of the opinion that U.S. Patent No. 6,740,669 B1 is eligible for extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a)

U.S. Patent No. 6,740,669 B1 claims a human drug product, rufinamide, and a pharmaceutical composition containing this human drug product.

b. 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

The term of U.S. Patent No. 6,740,669 B1 (expiring August 17, 2020) has not expired before the submission of this application.

c. 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of U.S. Patent No. 6,740,669 B1 has never been extended under 35 U.S.C. § 156.

d. 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

The Application for extension of the term of U.S. Patent No. 6,740,669 B1 is submitted by the authorized agent of the owner of record thereof in accordance with the requirements of 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

e. 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

The approved product, BANZEL™, has been subjected to a

regulatory review period before its commercial marketing or use.

f. 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(e)

The approved product, BANZEL™, has received permission for commercial marketing or use, and the permission for the commercial marketing or use of the product is the first such permission received under the Federal Food, Drug, and Cosmetic Act, Section 505 (21 U.S.C. § 355).

g. 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(h)

No other patent term has been extended for the same regulatory review period for the approved product, BANZEL™.

13. Length of Extension Claimed Under 37 C.F.R. § 1.740(a)(12)

The length of the extension of the patent term of U.S. Patent No. 6,740,669 B1 requested by Applicant is 819 days, i.e., to November 14, 2022, which length was calculated in accordance with 37 C.F.R. § 1.775 as follows:

a. The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on October 27, 1990 (30 days after the receipt date of the IND) and ended on November 14, 2008, amounting to a total of 6594 days, which is the sum of (i) and (ii) below:

   i) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", began on October 27, 1990 and ended on November 16, 2005, which is 5500 days;

   ii) The period for review under 35 U.S.C. § 156(g)(1)(B)(ii) the "Application Period", began on November 17, 2005 and ended on November 14, 2008, which is 1094 days;

b. The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in sub-paragraph (13)(a) above (6594 days) less:

   i) The number of days in the regulatory review period which were on and before the date on which the patent issued (May 25, 2004), i.e. 4960 days, and

   ii) The number of days during which the Applicant did not act with due diligence, i.e. zero days, and

   iii) One half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one half of (5500 - 4960) or 270 days;

which results in a period of 6594 - [4960 + 0 + 270] = 1364 days.

c. The number of days as determined in sub-paragraph (13)(b), when added to the original term, would result in the date of May 12, 2024.

d. Fourteen (14) years, when added to the date of the NDA Approved Letter (November 14, 2008), would result in the date of November 14, 2022.

e. The earlier date as determined by sub-paragraphs (13)(c) and (13)(d) is November 14, 2022.

f. Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five years. Five years, when added to the original expiration of U.S. Patent No. 6,740,669 B1 (August 17, 2020), results in the date of August 17, 2025.

g. The earlier date as determined in sub-paragraphs (13)(e) and (13)(f) is November 14, 2022, i.e., 819 days from the August 17, 2020 expiration date under 35 U.S.C. § 154.

14. Duty of Disclosure Acknowledgment under 37 C.F.R. § 1.740(a)(13)

Applicant acknowledges a duty to disclose to the U.S. Patent and Trademark Office and the Secretary of Health and Human Services any information, which is material to the determination of entitlement to the extension sought.

15. Fee Charge

The Commissioner is authorized to charge the prescribed fee for receiving and acting upon this application to Deposit Account 06-1205. Any overpayment should be credited to the same Deposit Account.

16. Correspondence Address Required by 37 C.F.R. § 1.740(a)(15)

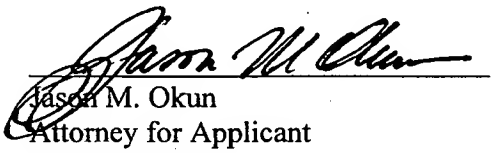
All correspondence relating to this application for patent term extension should be addressed to:

Jason M. Okun
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

17. Certification under 37 C.F.R. § 1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted with two additional copies thereof (for a total of three copies) in accordance with 37 C.F.R. § 1.740(b).

Respectfully submitted,



Jason M. Okun
Attorney for Applicant
Reg. No. 48,512

Date: January 12, 2008

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Telephone: (212) 218-2100
Facsimile: (212) 218-2200

APPENDIX A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent 6,740,669 B1

Issued: May 25, 2004

To: Robert Portmann, Urs Christoph Hofmeier, Andreas Burkhard, Walter Scherrer, and Martin Szelagiewicz

For: CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY

Sir:

Novartis AG, a company organized and existing under the laws of the Swiss Confederation, and having its registered office at Klybeckstrasse 141, CH-4057 Basel, Switzerland, being the owner of the entire title and interest in and to U.S. Patent No. 6,740,669 B1, which was granted on May 25, 2004 to Robert Portmann, Urs Christoph Hofmeier, Andreas Burkhard, Walter Scherrer, and Martin Szelagiewicz and entitled "CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC", hereby appoints the attorneys and agents associated with Customer No. 05514 as its agents to act in its interest in the Application for Patent Term Adjustment under 35 U.S.C. 156 of U.S. Patent No. 6,740,669 B1. A statement under 37 C.F.R. § 3.73(b) is provided herewith.

NOVARTIS AG

By: _____

Name: Daniel Woods

Title: Patent Attorney

Date: January 9, 2009

PTO/SB/96 (12-08)
Approved for use through 01/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Novartis AG

Application No./Patent No.: 6,740,669 B1 Filed/Issue Date: May 25, 2004

Entitled: CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

Novartis AG (Name of Assignee), a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [✓] the assignee of the entire right, title, and interest; or
2. [ ] an assignee of less than the entire right, title and interest (The extent (by percentage) of its ownership interest is _____ %)

in the patent application/patent identified above by virtue of either:

A. [✓] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 012696, Frame 0886, or for which a copy therefore is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.
2. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.
3. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Daniel Woods — Signature

1/9/09 — Date

Daniel Woods — Printed or Typed Name

862-778-9587 — Telephone Number

Patent Attorney — Title

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

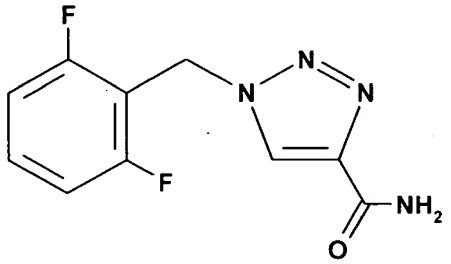
1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

APPENDIX B

BANZEL™
(rufinamide) Tablets

DESCRIPTION

BANZEL (rufinamide) is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs). Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide. It has an empirical formula of $C_{10}H_8F_2N_4O$ and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile.



BANZEL is available for oral administration in film-coated tablets, scored on both sides, containing 200 and 400 mg of rufinamide. Inactive ingredients are colloidal silicon dioxide, corn starch crosscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulphate. The film coating contains hypromellose, iron oxide red, polyethylene glycol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown.
The results of in vitro studies suggest that the principal mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Rufinamide (≥ 1 μM) significantly slowed sodium channel recovery from inactivation after a prolonged prepulse in cultured cortical neurons, and limited sustained repetitive firing of sodium-dependent action potentials (EC_{50} of 3.8 μM).

Pharmacokinetics

Overview

BANZEL is well absorbed after oral administration. However, the rate of absorption is relatively slow and the extent of absorption is decreased as dose is increased. The pharmacokinetics does not change with multiple dosing. Most elimination of rufinamide is via metabolism, with the primary metabolite resulting from enzymatic hydrolysis of the carboxamide moiety to form the carboxylic acid. This metabolic route is not cytochrome P450 dependent. There are no known active metabolites. Plasma half-life of rufinamide is approximately 6-10 hours.

Absorption and Distribution
Following oral administration of BANZEL, peak plasma concentrations occur between 4 and 6 hours (Tmax) both under fed and fasted conditions. BANZEL tablets display decreasing bioavailability with increasing dose after single and multiple dose administration. Based on urinary excretion, the extent of absorption was at least 85% following oral administration of a single dose of 600 mg rufinamide under fed conditions.

Multiple dose pharmacokinetics can be predicted from single dose data for both rufinamide and its metabolite. Given the dosing frequency of every 12 hours and the half life of 6 to 10 hours, the observed steady-state peak concentration of about two to three times the peak concentration after a single dose is expected.

Food increased the extent of absorption of rufinamide in healthy volunteers by 34% and increased peak exposure by 56% after a single dose of 400 mg, although the T_{max} was not elevated. Clinical trials were performed under fed conditions and dosing is recommended with food (see DOSAGE AND ADMINISTRATION).

Only a small fraction of rufinamide (34%) is bound to human serum proteins, predominantly to albumin (27%), giving little risk of displacement drug-drug interactions. Rufinamide was evenly distributed between erythrocytes and plasma. The apparent volume of distribution is dependent upon dose and varies with body surface area. The apparent volume of distribution was about 50 L at 3200 mg/day.

Metabolism
Rufinamide is extensively metabolized but has no active metabolites. Following a radiolabeled dose of rufinamide, less than 2% of the dose was recovered unchanged in urine. The primary biotransformation pathway is carboxylesterase(s) mediated hydrolysis of the carboxylamide group to the acid derivative CGP 47292. A few minor additional metabolites were detected in urine, which appeared to be acyl-glucuronides of CGP 47292. There is no involvement of oxidizing cytochrome P450 enzymes or glutathione in the biotransformation process.

Rufinamide is a weak inhibitor of CYP 2E1. It did not show significant inhibition of other CYP enzymes. Rufinamide is a weak inducer of CYP 3A4 enzymes.

Elimination/Excretion
Renal excretion is the predominant route of elimination for drug related material, accounting for 85% of the dose based on a radiolabeled study. Of the metabolites identified in urine, at least 66% of the rufinamide dose was excreted as the acid metabolite CGP 47292, with 2% of the dose excreted as rufinamide.

The plasma elimination half-life is approximately 6-10 hours in healthy subjects and patients with epilepsy.

Special Populations
Gender: Population pharmacokinetic analyses of females show a 6-14% lower apparent clearance of rufinamide compared to males. This effect is not clinically important.

Race: In a population pharmacokinetic analysis of clinical studies, no difference in clearance or volume of distribution of rufinamide was observed between the black and Caucasian subjects, after controlling for body size. Information on other races could not be obtained because of smaller numbers of these subjects.

Pediatrics: Based on a population analysis in 117 children (age 4-11 years) and 99 adolescents (age 12-17 years), the pharmacokinetics of rufinamide in these patients is similar to the pharmacokinetics in adults.

Elderly: The results of a study evaluating single-dose (400 mg) and multiple dose (800 mg/day for 6 days) pharmacokinetics of rufinamide in 8 healthy elderly subjects (65-80 years old) and 7 younger healthy subjects (18-45 years old) found no significant age-related differences in the pharmacokinetics of rufinamide.

Renal Impairment: Rufinamide pharmacokinetics in 9 patients with severe renal impairment (creatinine clearance <30 mL/min) was similar to that of healthy subjects. Patients undergoing dialysis 3 hours post rufinamide dosing showed a reduction in AUC and C_{max} by 29% and 16% respectively. Adjusting rufinamide dose for the loss of drug upon dialysis should be considered.

Hepatic Impairment: There have been no specific studies investigating the effect of hepatic impairment on the pharmacokinetics of rufinamide. Therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

Drug Interactions
Based on in vitro studies, rufinamide shows little or no inhibition of most cytochrome P450 enzymes at clinically relevant concentrations, with weak inhibition of CYP 2E1. Drugs that are substrates of CYP 2E1 (e.g. chlorzoxazone) may have increased plasma levels in the presence of rufinamide, but this has not been studied.

Based on in vivo drug interaction studies with triazolam and oral contraceptives, rufinamide is a weak inducer of the CYP 3A4 enzyme and can decrease exposure of drugs that are substrates of CYP 3A4. (see Effects of BANZEL on other medications)

Rufinamide is metabolized by carboxylesterases. Drugs that may induce the activity of carboxylesterases may increase the clearance of rufinamide. Broad-spectrum inducers such as carbamazepine and phenobarbital may have minor effects on rufinamide metabolism via this mechanism. Drugs that are inhibitors of carboxylesterases may decrease metabolism of rufinamide.

Antiepileptic Drugs

Effects of BANZEL on other AEDs

Population pharmacokinetic analysis of average concentration at steady state of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate showed that typical rufinamide C_{avss} levels had little effect on the pharmacokinetics of other AEDs. Any effects, when they occur, have been more marked in the pediatric population.

Table 1 summarizes the drug-drug interactions of BANZEL with other AEDs.

Table 1: Summary of drug-drug interactions of BANZEL with other anti-epileptic drugs

AED Co-administered	Influence of Rufinamide on AED concentration [a)]	Influence of AED on Rufinamide concentration
Carbamazepine	**Decrease by 7 to 13%** [b)]	**Decrease by 19 to 26%** Dependent on dose of carbamazepine
Lamotrigine	**Decrease by 7 to 13%** [b)]	**No Effect**
Phenobarbital	**Increase by 8 to 13%** [b)]	**Decrease by 25 to 46%** [c), d)] Independent of dose or concentration of phenobarbital
Phenytoin	**Increase by 7 to 21%** [b)]	**Decrease by 25 to 46%** [c), d)] Independent of dose or concentration of phenytoin
Topiramate	**No Effect**	**No Effect**
Valproate	**No Effect**	**Increase by <16 to 70%** [c)] Dependent on concentration of valproate
Primidone	Not Investigated	**Decrease by 25 to 46%** [c), d)] Independent of dose or concentration of primidone
Benzodiazepines [e)]	Not Investigated	**No Effect**

a) Predictions are based on BANZEL concentrations at the maximum recommended dose of BANZEL.

b) Maximum changes predicted to be in children and in patients who achieve significantly higher levels of BANZEL, as the effect of rufinamide on these AEDs is concentration-dependent.

c) Larger effects in children at high doses/concentrations of AEDs.

d) Phenobarbital, primidone and phenytoin were treated as a single covariate (phenobarbital-type inducers) to examine the effect of these agents on BANZEL clearance.

e) All compounds of the benzodiazepine class were pooled to examine for 'class effect' on BANZEL clearance.

Phenytoin: The decrease in clearance of phenytoin estimated at typical levels of rufinamide (C_{avss} 15 μg/mL) is predicted to increase plasma levels of phenytoin by 7 to 21%. As phenytoin is known to have non-linear pharmacokinetics (clearance becomes saturated at higher doses), it is possible that exposure will be greater than the model prediction.

Effects of Other AEDs on BANZEL

Potent cytochrome P450 enzyme inducers, such as carbamazepine, phenytoin, primidone, and phenobarbital appear to increase the clearance of BANZEL (see Table 1). Given that the majority of clearance of BANZEL is via a non-CYP-dependent route, the observed decreases in blood levels seen with carbamazepine phenytoin, phenobarbital, and primidone are unlikely to be entirely attributable to induction of a P450 enzyme. Other factors explaining this interaction are not understood.

Any effects, where they occurred were likely to be more marked in the pediatric population.

Valproate: Based on a population pharmacokinetic analysis, rufinamide clearance was decreased by valproate. In children, valproate administration may lead to elevated levels of rufinamide by up to 70%. Patients stabilized on BANZEL before being prescribed valproate should begin valproate therapy at a low dose, and titrate to a clinically effective dose. Similarly, patients on valproate should begin at a BANZEL dose lower than 400 mg.

Effects of BANZEL on other Medications

Hormonal contraceptives: Co-administration of BANZEL (800 mg BID for 14 days) and Ortho-Novum 1/35® resulted in a mean decrease in the ethinyl estradiol AUC_{0-24} of 22% and C_{max} by 18% and norethindrone AUC_{0-24} by 14% and C_{max} by 18%, respectively. The clinical significance of this decrease is unknown. Female patients of childbearing age should be warned that the concurrent use of BANZEL with hormonal contraceptives may render this method of contraception less effective. Additional non-hormonal forms of contraception are recommended when using BANZEL (see Information for Patients).

Triazolam: Co-administration and pre-treatment with BANZEL (400 mg bid) resulted in a 37% decrease in AUC and a 23% decrease in C_{max} of triazolam, a CYP 3A4 substrate.

Olanzapine: Co-administration and pre-treatment with BANZEL (400mg bid) resulted in no change in AUC and C_{max} of olanzapine, a CYP 1A2 substrate.

CLINICAL STUDIES

The effectiveness of BANZEL as adjunctive treatment for the seizures associated with Lennox-Gastaut syndrome (LGS) was established in a single multicenter, double-blind, placebo-controlled, randomized, parallel-group study (n=138). Male and female patients

(between 4 and 30 years of age) were included if they had a diagnosis of inadequately controlled seizures associated with LGS (including both atypical absence seizures and drop attacks) and were being treated with 1 to 3 concomitant stable dose AEDs. Each patient must have had at least 90 seizures in the month prior to study entry. After completing a 4 week Baseline Phase on stable therapy, patients were randomized to have BANZEL or placebo added to their ongoing therapy during the 12 week Double-blind Phase. The Double-blind Phase consisted of 2 periods: the Titration Period (1 to 2 weeks) and the Maintenance Period (10 weeks). During the Titration Period, the dose was increased to a target dosage of approximately 45 mg/kg/day (3200 mg in adults of $\geq$ 70kg), given on a b.i.d. schedule. Dosage reductions were permitted during titration if problems in tolerability were encountered. Final doses at titration were to remain stable during the maintenance period. Target dosage was achieved in 88% of the BANZEL-treated patients. The majority of these patients reached the target dose within 7 days, with the remaining patients achieving the target dose within 14 days.

The primary efficacy variables were:

- The percent change in total seizure frequency per 28 days;
- The percent change in tonic-atonic (drop attacks) seizure frequency per 28 days;
- Seizure severity from the Parent/Guardian Global Evaluation of the patient's condition. This was a 7-point assessment performed at the end of the Double-blind Phase. A score of +3 indicated that the patient's seizure severity was very much improved, a score of 0 that the seizure severity was unchanged, and a score of -3 that the seizure severity was very much worse.

The results of the three primary endpoints are shown in Table 2 below.

Table 2:Lennox-Gastaut Syndrome Trial Seizure Frequency Primary Efficacy Variable Results

Variable	Placebo	Rufinamide
Median percent change in total seizure frequency per 28 days	-11.7	-32.7 (p=0.0015)
Median percent change in tonic-atonic seizure frequency per 28 days	1.4	-42.5 (p<0.0001)
Improvement in Seizure Severity Rating from Global Evaluation	30.6	53.4 (p=0.0041)

INDICATIONS AND USAGE

BANZEL (rufinamide) is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults.

CONTRAINDICATIONS

BANZEL is contraindicated in patients with Familial Short QT syndrome (See PRECAUTIONS, QT Shortening).

WARNINGS

Suicidal Behavior and Ideation

Antiepileptic drugs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any antiepileptic drug for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different antiepileptic drugs showed that patients randomized to one of the antiepileptic drugs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 antiepileptic drug-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior was observed as early as one week after starting drug treatment and persisted for at least 24 weeks. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with antiepileptic drugs of varying mechanisms of action and across a range of indications suggests that the risk applies to all antiepileptic drugs used for any indication. The risk did not vary substantially by age in the clinical trials analyzed.

The following table (Table 3) shows absolute and relative risk of suicidal behavior and ideation by indication.

Table 3: Absolute and Relative Risk of Suicidal Behavior and Ideation

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar.

Anyone considering prescribing BANZEL or any other antiepileptic drug must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which antiepileptics are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Central Nervous System Reactions:

Use of BANZEL has been associated with central nervous system-related adverse reactions. The most significant of these can be classified into two general categories:
1) somnolence or fatigue, and 2) coordination abnormalities, dizziness, gait disturbances, and ataxia (see ADVERSE REACTIONS).

PRECAUTIONS

QT Shortening
Formal cardiac ECG studies demonstrated shortening of the QT interval (up to 20 msec) with BANZEL treatment. In a placebo-controlled study of the QT interval, a higher percentage of BANZEL-treated subjects (46% at 2400 mg, 46% at 3200 mg, and 65% at 4800 mg) had a QT shortening of greater than 20 msec at Tmax compared to placebo (5 – 10%).

Reductions of the QT interval below 300 msec were not observed in the formal QT studies with doses up to 7200 mg/day. Moreover, there was no signal for drug-induced sudden death or ventricular arrhythmias.

The degree of QT shortening induced by BANZEL is without any known clinical risk. Familial Short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 msec. Nonclinical data also indicate that QT shortening is associated with ventricular fibrillation.

Patients with Familial Short QT syndrome should not be treated with BANZEL (see Contraindications). Caution should be used when administering BANZEL with other drugs that shorten the QT interval.

Multi-organ Hypersensitivity Reactions
Multi-organ hypersensitivity syndrome, a serious condition sometimes induced by antiepileptic drugs, has occurred in association with BANZEL therapy in clinical trials. One patient experienced rash, urticaria, facial edema, fever, elevated eosinophils, stuporous state, and severe hepatitis, beginning on day 29 of BANZEL therapy and extending over a course of 30 days of continued BANZEL therapy with resolution 11 days after discontinuation. Additional possible cases presented with rash and one or more of the following: fever, elevated liver function studies, hematuria, and lymphadenopathy. These cases occurred in children less than 12 years of age, within four weeks of treatment initiation, and were noted to resolve and/or improve upon BANZEL discontinuation. This syndrome has been reported with other anticonvulsants and typically, although not exclusively, presents with fever and rash associated with other organ system involvement. Because this disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. If this reaction is suspected, BANZEL should be discontinued and alternative treatment started.

All patients who develop a rash while taking BANZEL must be closely supervised.

Withdrawal of AEDs
As with all antiepileptic drugs BANZEL should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus. If abrupt discontinuation of the drug is medically necessary, the transition to another AED should be made under close medical supervision. In clinical trials BANZEL discontinuation was achieved by reducing the dose by approximately 25% every two days.

Status Epilepticus
Estimates of the incidence of treatment emergent status epilepticus among patients treated with BANZEL are difficult because standard definitions were not employed. In a controlled Lennox Gastaut syndrome trial, 3 of 74 (4.1 %) BANZEL-treated patients had episodes that could be described as status epilepticus in the BANZEL-treated patients compared with none of the 64 patients in the placebo-treated patients. In all controlled trials that included patients with different epilepsies, 11 of 1240 (0.9%) BANZEL-treated patients had episodes that could be described as status epilepticus compared with none of 635 patients in the placebo-treated patients.

Information for Patients
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with BANZEL and should counsel them in its appropriate use. A patient Medication Guide is available for BANZEL. The prescriber or healthcare professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking BANZEL.

Suicidal Thinking and Behavior - Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Patients should be instructed to take BANZEL only as prescribed.

BANZEL should be taken with food.

As with all centrally-acting medications, alcohol in combination with BANZEL may cause additive central nervous system effects.

Patients should be advised about the potential for somnolence or dizziness and advised not to drive or operate machinery until they have gained sufficient experience on BANZEL to gauge whether it adversely affects their mental and/or motor performance.

Female patients of childbearing age should be warned that the concurrent use of BANZEL with hormonal contraceptives may render this method of contraception less effective (see Drug Interactions). Additional non-hormonal forms of contraception are recommended when using BANZEL.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding or intend to breast-feed.

Patients should be advised to notify their physician if they experience a rash associated with fever.

Laboratory Tests
Leucopenia (white cell count < $3X10^9$ L) was more commonly observed in BANZEL-treated patients (43 of 1171, 3.7%) than placebo-treated patients (7 of 579, 1.2%) in all controlled trials.

Drug Interactions
In vitro and in vivo studies have shown that BANZEL is unlikely to be involved in significant pharmacokinetic interactions.

BANZEL can increase plasma concentrations of phenytoin by 21% or more due to non linear pharmacokinetics.

Valproate can increase BANZEL concentrations up to 70%. Patients stabilized on BANZEL before being prescribed valproate should begin valproate therapy at a low dose, and titrate to

a clinically effective dose. Similarly, patients on valproate should begin at a BANZEL dose lower than 400 mg.

Coadministration of BANZEL with ethinyl estradiol and norethindrone can decrease AUC_{0-24} of these hormonal contraceptives by 22% and 14% and C_{max} by 31% and 18%, respectively. Female patients of childbearing age should be warned that the concurrent use of BANZEL with hormonal contraceptives may render this method of contraception less effective. Additional non-hormonal forms of contraception are recommended when using BANZEL. (see CLINICAL PHARMACOLOGY and Information for Patients)

Drug/Laboratory Test Interactions
There are no known interactions of BANZEL with commonly used laboratory tests.

Carcinogenicity, Mutagenicity, Impairment of Fertility
Carcinogenicity: Rufinamide was given in the diet to mice at 40, 120, and 400 mg/kg/day and to rats at 20, 60, and 200 mg/kg/day for two years. The doses in mice were associated with plasma AUCs 0.1 to 1 times the human plasma AUC at the maximum recommended human dose (MRHD, 3200 mg/day). Increased incidences of tumors (benign bone tumors (osteomas) and/or hepatocellular adenomas and carcinomas) were observed in mice at all doses. Increased incidences of thyroid follicular adenomas were observed in rats at all but the low dose; the low dose is <0.1 times the MRHD on a mg/m^2 basis.

Mutagenicity: Rufinamide was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or the in vitro mammalian cell point mutation assay. Rufinamide was not clastogenic in the in vitro mammalian cell chromosomal aberration assay or the in vivo rat bone marrow micronucleus assay.

Impairment of Fertility: Oral administration of rufinamide (doses of 20, 60, 200, and 600 mg/kg/day) to male and female rats prior to mating and throughout mating, and continuing in females up to day 6 of gestation resulted in impairment of fertility (decreased conception rates and mating and fertility indices; decreased numbers of corpora lutea, implantations, and live embryos; increased preimplantation loss; decreased sperm count and motility) at all doses tested. Therefore, a no-effect dose was not established. The lowest dose tested was associated with a plasma AUC $\approx$ 0.2 times the human plasma AUC at the MRHD.

PREGNANCY

Pregnancy Category C
Rufinamide produced developmental toxicity when administered orally to pregnant animals at clinically relevant doses.

Rufinamide was administered orally to rats at doses of 20, 100, and 300 mg/kg/day and to rabbits at doses of 30, 200, and 1000 mg/kg/day during the period of organogenesis (implantation to closure of the hard palate); the high doses are associated with plasma AUCs $\approx$2 times the human plasma AUC at the maximum recommended human dose (MRHD, 3200 mg/day). Decreased fetal weights and increased incidences of fetal skeletal abnormalities

were observed in rats at doses associated with maternal toxicity. In rabbits, embryo-fetal death, decreased fetal body weights, and increased incidences of fetal visceral and skeletal abnormalities occurred at all but the low dose. The highest dose tested in rabbits was associated with abortion. The no-effect doses for adverse effects on rat and rabbit embryo-fetal development (20 and 30 mg/kg/day, respectively) were associated with plasma AUCs ≈ 0.2 times that in humans at the MRHD).

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at oral doses of 5, 30, and 150 mg/kg/day (associated with plasma AUCs up to ≈1.5 times that in humans at the MRDH), decreased offspring growth and survival were observed at all doses tested. A no-effect dose for adverse effects on pre- and post-natal development was not established. The lowest dose tested was associated with plasma AUC < 0.1 times that in humans at the MRHD.

There are no adequate and well-controlled studies in pregnant women. BANZEL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of BANZEL on labor and delivery in humans is not known.

Nursing Mothers
Rufinamide is likely to be excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from BANZEL, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness in patients with Lennox-Gastaut syndrome have not been established in children less than 4 years.

Geriatric Use
Clinical studies of BANZEL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

A study evaluating the pharmacokinetics of rufinamide in elderly subjects showed that there were no significant differences in the plasma and urine pharmacokinetic parameters of rufinamide between the younger and elderly subjects under both single and multiple dose treatments. (See Special Populations: Elderly).

ADVERSE REACTIONS

Placebo-controlled double-blind studies were performed in adults and in pediatric patients, down to age of 4, in other forms of epilepsy, in addition to the trial in Lennox-Gastaut

syndrome. Data on CNS Reactions (see WARNINGS) from the Lennox-Gastaut study are presented first. Because there is no reason to suspect that adverse reactions would substantially differ between these patient populations, safety data from all of these controlled studies are then presented. Most of these adverse reactions were mild to moderate and transient in nature.

Common central nervous system reactions in the controlled trial of patients 4 years or older with Lennox Gastaut syndrome treated with BANZEL as adjunctive therapy (see WARNINGS):

Somnolence was reported in 24.3% of BANZEL-treated patients compared to 12.5% of placebo patients and led to study discontinuation in 2.7% of treated patients compared to 0% of placebo patients. Fatigue was reported in 9.5% of BANZEL-treated patients compared to 7.8% of placebo patients. It led to study discontinuation in 1.4% of treated patients and 0% of placebo patients.

Dizziness was reported in 2.7% of BANZEL-treated patients compared to 0% of placebo patients, and did not lead to study discontinuation.

Ataxia and gait disturbance were reported in 5.4% and 1.4% of BANZEL-treated patients, respectively, and in no placebo patients. Balance disorder and abnormal coordination were each reported in 0% of BANZEL-treated patients and 1.6% of placebo patients. None of these reactions led to study discontinuation.

All Adverse Reactions for All Treated Patients with Epilepsy, Double-blind Adjunctive Therapy Studies: The most commonly observed (≥10%) adverse reactions in BANZEL-treated patients, when used as adjunctive therapy at all doses studied (200 to 3200 mg/day) with a higher frequency than in placebo were: headache, dizziness, fatigue, somnolence, and nausea.

At the target dose of 45 mg/kg/day in children, the most commonly observed (≥5%) adverse reactions in BANZEL-treated patients, given as adjunctive therapy, with a higher frequency than placebo were: somnolence, vomiting, headache, fatigue, dizziness, nausea, and convulsion.

At doses up to 3200 mg/day in adults, the most commonly observed (≥5%) adverse reactions in BANZEL-treated patients, given as adjunctive therapy, at all doses studied, with a higher frequency than placebo were: headache, dizziness, fatigue, nausea, somnolence, diplopia, nasopharyngitis, tremor, nystagmus, vision blurred and vomiting.

Table 4 lists treatment-emergent adverse reactions that occurred in at least 3% of pediatric patients with epilepsy treated with BANZEL in controlled adjunctive studies and were numerically more common in patients treated with BANZEL than placebo.

Table 4: Incidence (%) of Treatment-Emergent Adverse Reactions in all Pediatric Double-Blind Adjunctive Trials by Preferred Term at the Recommended Dose of 45 mg/kg/day (Adverse Reactions occurred in at least 3% of BANZEL-treated patients and occurred more frequently than in Placebo Patients)

Preferred Term	BANZEL (N=187) %	Placebo (N=182) %
Somnolence	17	9
Vomiting	17	7
Headache	16	8
Fatigue	9	8
Dizziness	8	6
Nausea	7	3
Influenza	5	4
Nasopharyngitis	5	3
Decreased Appetite	5	2
Rash	4	2
Ataxia	4	1
Diplopia	4	1
Bronchitis	3	2
Sinusitis	3	2
Psychomotor Hyperactivity	3	1
Abdominal Pain Upper	3	2
Aggression	3	2
Ear Infection	3	1
Disturbance in Attention	3	1
Pruritis	3	0

Table 5 lists treatment-emergent adverse reactions that occurred in at least 3% of adult patients with epilepsy treated with BANZEL (up to 3200mg/day) in adjunctive controlled studies and were numerically more common in patients treated with BANZEL than placebo. In these studies, either BANZEL or placebo was added to current AED therapy.

Table 5: Incidence (%) of Treatment-Emergent Adverse Reactions in all Adult Double-Blind Adjunctive Trials (up to 3200mg/day) by Preferred Term (Adverse Reactions occurred in at least 3% of BANZEL-treated patients and occurred more frequently than in Placebo Patients)

Preferred Term	BANZEL (N=823) %	Placebo (N=376) %
Headache	27	26
Dizziness	19	12
Fatigue	16	10
Nausea	12	9

Somnolence	11	9
Diplopia	9	3
Tremor	6	5
Nystagmus	6	5
Vision Blurred	6	2
Vomiting	5	4
Ataxia	4	0
Abdominal Pain Upper	3	2
Anxiety	3	2
Constipation	3	2
Dyspepsia	3	2
Back Pain	3	1
Gait Disturbance	3	1
Vertigo	3	1

Discontinuation in Controlled Clinical Studies

In controlled double-blind adjunctive clinical studies, 9.0% of patients receiving BANZEL as adjunctive therapy and 4.4% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions most commonly leading to discontinuation of BANZEL (>1%) used as adjunctive therapy were generally similar in adults and children.

In pediatric double-blind adjunctive clinical studies, 8.0% of patients receiving BANZEL as adjunctive therapy and 2.2% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions most commonly leading to discontinuation of BANZEL (>1%) used as adjunctive therapy are presented in Table 6.

Table 6: Adverse Reactions Most Commonly Leading to Discontinuation in Double-Blind Adjunctive Trials (At The Recommended Dose of 45mg/kg/day) In Pediatric Patients

Preferred Term	BANZEL (N=187) %	Placebo (N=182) %
Convulsion	2	1
Rash	2	1
Fatigue	2	0
Vomiting	1	0

In adult double-blind adjunctive clinical studies (up to 3200 mg/day), 9.5% of patients receiving BANZEL as adjunctive therapy and 5.9% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions most commonly leading to discontinuation of BANZEL (>1%) used as adjunctive therapy are presented in Table 7.

Table 7: Adverse Reactions Most Commonly Leading to Discontinuation in Double-Blind Adjunctive Trials (up to 3200 mg/day) In Adult Patients

Preferred Term	BANZEL (N=823) %	Placebo (N=376) %
Dizziness	3	1
Fatigue	2	1
Headache	2	1
Nausea	1	0
Ataxia	1	0

Other Adverse Events Observed During Clinical Trials:

BANZEL has been administered to 1978 individuals during all epilepsy clinical trials (placebo-controlled and open-label). Adverse events occurring during these studies were recorded by the investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of patients having adverse events, these events were grouped into standardized categories using the MedDRA dictionary. Adverse events occurring at least three times and considered possibly related to treatment are included in the System Organ Class listings below. Terms not included in the listings are those already included in the tables above, those too general to be informative, those related to procedures, and terms describing events common in the population. Some events occurring fewer than 3 times are also included based on their medical significance. Because the reports include events observed in open label, uncontrolled observations, the role of BANZEL in their causation cannot be reliably determined.

Events are classified by body system and listed in order of decreasing frequency as follows: *frequent adverse events*- those occurring in at least 1/100 patients; *infrequent adverse events*- those occurring in 1/100 to 1/1000 patients; *rare*- those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders: *Frequent*: anemia. *Infrequent*: lymphadenopathy, leukopenia, neutropenia, iron deficiency anemia, thrombocytopenia.

Cardiac Disorders: *Infrequent:* bundle branch block right, atrioventricular block first degree

Metabolic and Nutritional Disorders: *Frequent:* decreased appetite, increased appetite.
Renal and Urinary Disorders: *Frequent:* pollakiuria. *Infrequent:* urinary incontinence, dysuria, hematuria, nephrolithiasis, polyuria, enuresis, nocturia, incontinence.

DRUG ABUSE AND DEPENDENCE
The abuse and dependence potential of BANZEL has not been evaluated in human studies.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Certified Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

One overdose of 7200 mg/day BANZEL was reported in an adult during the clinical trials. The overdose was associated with no major signs or symptoms, no medical intervention was required, and the patient continued in the study at the target dose.

Treatment or Management of Overdose: There is no specific antidote for overdose with BANZEL. If clinically indicated, elimination of unabsorbed drug should be attempted by induction of emesis or gastric lavage. Usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Hemodialysis: Standard hemodialysis procedures may result in limited clearance of rufinamide. Although there is no experience to date in treating overdose with hemodialysis, the procedure may be considered when indicated by the patient's clinical state.

DOSAGE AND ADMINISTRATION

Children four years and older with Lennox-Gastaut syndrome: Treatment should be initiated at a daily dose of approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a target dose of 45 mg/kg/day or 3200 mg/day, whichever is less, administered in two equally divided doses. It is not known whether doses lower than the target doses are effective.

Adults with Lennox-Gastaut syndrome: Treatment should be initiated at a daily dose of 400-800 mg/day administered in two equally divided doses. The dose should be increased by 400-800 mg/day every 2 days until a maximum daily dose of 3200 mg/day, administered in two equally divided doses is reached. It is not known whether doses lower than 3200 mg are effective.

BANZEL tablets are scored on both sides and can be cut in half for dosing flexibility. Tablets can be administered whole, as half tablets or crushed.

BANZEL should be given with food.

Patients with Renal Impairment

Renally impaired patients (creatinine clearance less than 30 mL/min) do not require any special dosage change when taking BANZEL.

Patients Undergoing Hemodialysis

Hemodialysis may reduce exposure to a limited (about 30%) extent. Accordingly, adjusting the BANZEL dose during the dialysis process can be considered.

Patients with Hepatic Disease
Use of BANZEL in patients with hepatic impairment has not been studied. Therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

HOW SUPPLIED
BANZEL 200 mg tablets (containing 200 mg rufinamide) are pink in color, film-coated, oblong-shape tablets, with a score on both sides, imprinted with "Є 262" on one side. They are available in bottles of 30 (NDC 62856-582-30).

BANZEL 400 mg tablets (containing 400 mg rufinamide) are pink in color, film-coated, oblong-shape tablets, with a score on both sides, imprinted with "Є 263" on one side. They are available in bottles of 120 (NDC 62856-583-52).

Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°F - 86°F). Protect from moisture. Replace cap securely after opening.

Rx Only

BANZEL™ is a trademark of Novartis Pharma AG, used under license.

Manufactured by Eisai Co., Ltd.

Marketed by Eisai Inc., Woodcliff Lake, NJ 07677

Medication Guide

BANZEL™ (ban-'zel)

[rufinamide]

BANZEL and Suicidal Thoughts or Actions

Read this Medication Guide before you start taking BANZEL and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. This Medication Guide is only about the risk of suicidal thoughts and actions with BANZEL.

What is the most important information I should know about BANZEL?

1. **BANZEL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

2. **Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**
   - thoughts about suicide or dying
   - attempt to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

3. **Do not stop BANZEL without first talking to a healthcare provider.**
   - Stopping BANZEL suddenly can cause serious problems.
   - Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

4. **How can I watch for early symptoms of suicidal thoughts and actions?**
   - Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled.

- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

What else should I know about BANZEL?

- **BANZEL has other side effects.** For more information ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers you.

  Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

- **BANZEL can interact with other medicines.** Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Using BANZEL with certain other medicines can affect each other causing side effects.

  Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without first talking with your healthcare provider.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BANZEL for a condition for which it was not prescribed. Do not give BANZEL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about BANZEL. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about BANZEL that is written for health professionals.

For more information, go to www.banzel.com or call 1-888-274-2378.

Issued November 2008

This Medication Guide has been approved by the U.S. Food and Drug administration

Manufactured by Eisai Co., Ltd.
Marketed by Eisai Inc., Woodcliff Lake, NJ 07677

APPENDIX C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-911

NDA APPROVAL

Eisai Medical Research, Inc.
Attention: Joseph Zuccarini, Pharm.D.
Associate Director Regulatory Affairs
55 Challenger Road
Ridgefield Park, NJ 07660

Dear Mr. Zuccarini,

Please refer to your new drug application (NDA) dated November 17, 2005, received November 17, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Banzel (rufinamide) Tablets, 100, 200, and 400 mg.

We acknowledge receipt of your submissions dated February 29, April 1 and 11, May 8, July 22 and 25, August 5, 19, 20, 25, and 28, September 10, 15, 22, and 25, October 10, 16, 17, and 23, and November 3, 7, and 10, 2008.

The February 29, 2008 submission constituted a complete response to our September 15, 2006 action letter.

This new drug application provides for the use of Banzel (rufinamide) for adjunctive therapy of seizures associated with Lennox-Gastaut syndrome.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain

purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks of the potential for QT shortening in the setting of concomitant medications that may also have a QT shortening effect, the inhibitory effect of Banzel (rufinamide) on P-gp, and adverse effects on postnatal growth and development.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these unexpected serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial.

1. Conduct additional analyses to further examine the effect of Banzel (rufinamide) on the QT interval, specifically studying its effect in patients receiving concomitant medications that may also shorten the QT interval. For clinical trials AE/ET1 and CRUF331-0022 (and any other trials in which patients were treated with medications other than rufinamide and in which QT data was collected), please provide the following:
    a. The baseline (pre-treatment) mean QT interval (as measured by all three correction methods) in rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval (listed below) and in patients without such concomitant medications.
    b. The mean on-treatment QT interval (again by all three correction methods) for rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval and in patients without such concomitant medications.

    Conduct the same analysis for sodium channel blocking drugs. These drugs are also listed below.

    QT-SHORTENING DRUGS:

    1. Digoxin (Lanoxin ®, Digitek ®, Lanoxicaps ®)
    2. Lamotrigine (Lamictal ®)
    3. Ranolazine (Ranexa ®)
    4. Mexiletine (Mexitil ®)
    5. Magnesium

    SODIUM CHANNEL BLOCKING DRUGS:

    1. Procainamide (Pronestyl ®, Procan ®, Procanbid ®)
    2. Disopryamide (Norpace ®)
    3. Tocainide (Tonocard ®)
    4. Mexiletine (Mexitil ®)
    5. Phenytoin (Phenytek ®, Dilantin ®, Eptoin ®, Epanutin ®)
    6. Flecainide (Tambocor ®, Almarytm ®, Apocard ®, Ecrinal ®, and Flécaine ®)

7. Propafenone (Rythmol SR ®, Rytmonorm ®)
8. Moricizine
9. Lidocaine
10. Propofol
11. Carbamazepine (Tegreto ®, Biston ®, Calepsin ®, Carbatrol ®, Epitol ®, Equetro ®, Finlepsin ®, Sirtal ®, Stazepine ®, Telesmin ®,Teril ®, Timonil ®, Epimaz ®, Degranol ®)
12. Amitriptyline (Elavil ®, Tryptanol ®, Endep ®, Elatrol ®, Tryptizol ®, Trepiline ®, Laroxy ®l, Saroten ®, Triptyl ®)
13. Imipramine (Antideprin ®, Deprenil ®, Deprimin ®, Deprino ®l, Depsonil ®, Dynaprin ®, Eupramin ®, Imipramil ®, Irmin ®, Janimine ®, Melipramin ®, Surplix ®, Tofranil ®)
14. Haloperidol (Aloperidin ®, Bioperidolo ®, Brotopon ®, Dozic ®, Duraperidol ® , Einalon ® Eukystol ®, Haldol ®, Halosten®
15. Chlorpromazine
16. Digoxin (Lanoxin ®, Digitek ®, Lanoxicaps ®)
17. Metoclopramide (Maxolon ®, Reglan ®, Degan ®, Maxeran ®, Primperan ®, Pylomid ®)
18. Isoproterenol

Final Report Submission: by January 2009

In addition, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a the following studies.

2. Conduct an *in vitro* metabolism study to characterize the potential serious safety risk of the inhibitory effect of Banzel (rufinamide) on P-gp.

Protocol Submission:	by June 2009
Study Start Date:	by August 2009
Final Report Submission:	by December 2009

3. Conduct a juvenile dog toxicology study to identify the unexpected serious risk of adverse effects on postnatal growth and development.

Protocol Submission:	by June 2009
Study Start Date:	by September 2009
Final Report Submission:	by January 2011

Submit the protocols to your IND 35,534 with a cross-reference letter to this NDA 21-911. Submit all final reports to your NDA 21-911. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Banzel (rufinamide) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Banzel (rufinamide). FDA has determined that Banzel (rufinamide) has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Banzel (rufinamide). In addition, patient labeling could help prevent serious adverse effects related to the use of these products. Banzel (rufinamide) may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Banzel (rufinamide).

Your proposed REMS, submitted on October 24, 2008, in an electronic communication, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your October 24, 2008 submission.

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Banzel (rufinamide)
b. A report on periodic assessments of the distribution and dispending of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 21-911 REMS ASSESSEMENT**
- **NEW SUPPLEMENT FOR NDA 21-911**
- **PROPOSED REMS MODIFICATION**

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-911."

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

CARTON AND IMMEDIATE CONTAINER LABELS

Please refer to our correspondence, dated September 3, 2008, requesting that the following revisions be made to the labels:

(b) (4)

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-911**." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

Rufinamide was not referred to an Advisory Committee for review because it is not the first in its class (antiepileptic drugs), an evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the results of the efficacy trial in Lennox-Gastaut Syndrome combined with data from studies in partial seizures did not pose concerns for the use of rufinamide for Lennox-Gastaut Syndrome.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
11/14/2008 05:04:21 PM

APPENDIX D

US006740669B1

(12) **United States Patent**
Portmann et al.

(10) **Patent No.: US 6,740,669 B1**
(45) **Date of Patent: May 25, 2004**

(54) **CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC**

(75) Inventors: **Robert Portmann**, Pratteln (CH); **Urs Christoph Hofmeier**, St. Pantaleon (CH); **Andreas Burkhard**, Basel (CH); **Walter Scherrer**, Rheinfelden (CH); **Martin Szelagiewicz**, Münchenstein (CH)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 801 days.

(21) Appl. No.: **09/125,329**

(22) PCT Filed: **Jun. 8, 1998**

(86) PCT No.: **PCT/EP98/03427**

§ 371 (c)(1),
(2), (4) Date: **Sep. 8, 1998**

(87) PCT Pub. No.: **WO98/56772**

PCT Pub. Date: **Dec. 17, 1998**

(30) **Foreign Application Priority Data**

Jun. 10, 1997 (CH) 1404/97

(51) **Int. Cl.**[7] **A61K 31/4192**; C07D 249/04
(52) **U.S. Cl.** **514/359**; 548/255
(58) **Field of Search** 514/359; 548/255

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,789,680 A * 12/1988 Meier 514/359

FOREIGN PATENT DOCUMENTS

EP 199 262 A 10/1986

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Munzel II, Progress in Drug Research, 14 (1970) pp. 309–321, XP 0020785047 Basel, CH.*

Munzel K., Progress in Drug Research, vol. 10, pp. 227–330 (1966).

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Chemical & Engineering News, pp. 32–34 (2003).

U.S. Pharmacopia, pp. 1843 & 1844 (1995).

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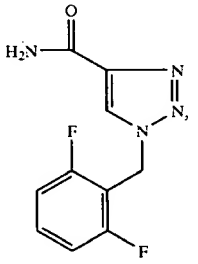
* cited by examiner

Primary Examiner—Patricia L. Morris
(74) *Attorney, Agent, or Firm*—Joseph J. Borovian

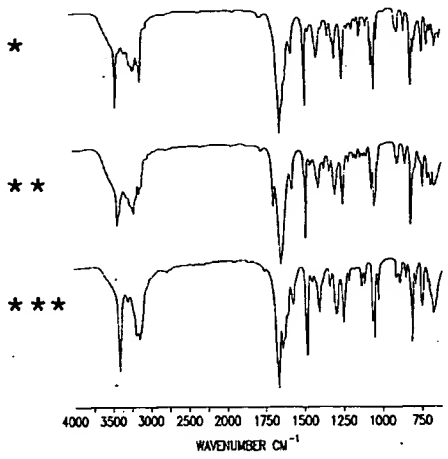
(57) **ABSTRACT**

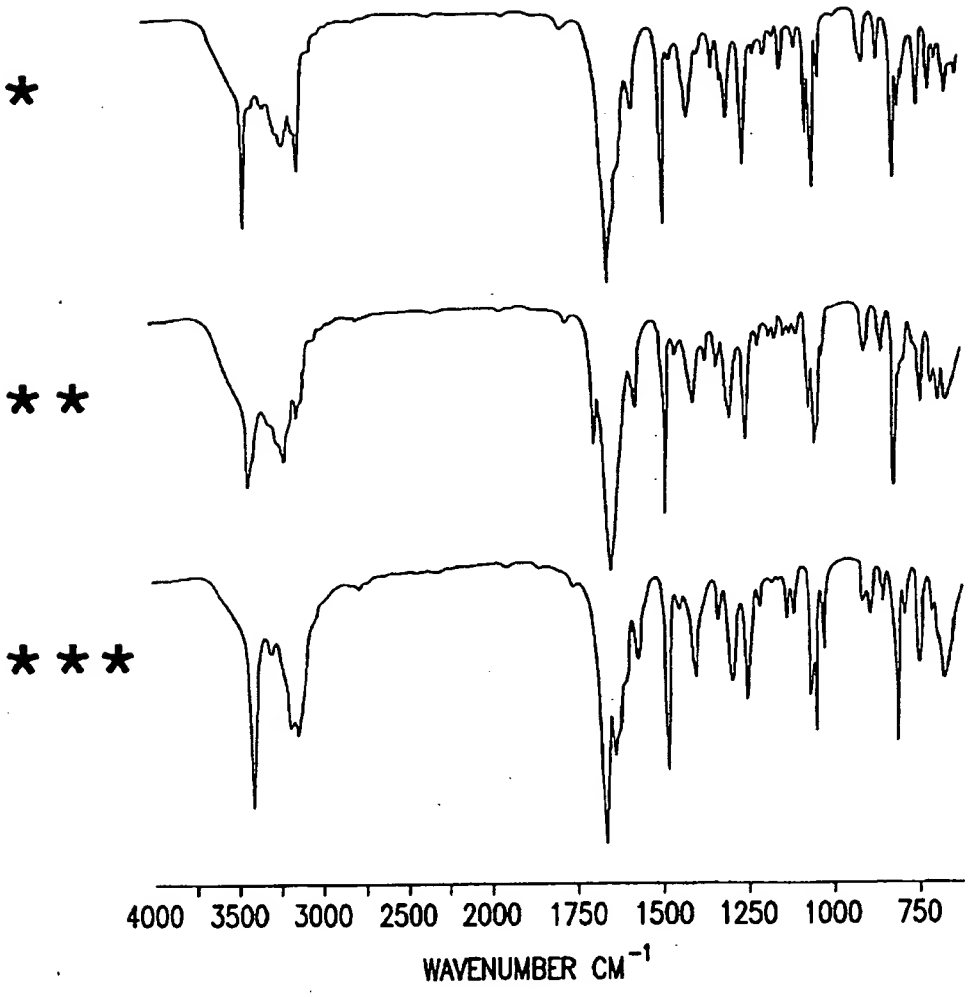
The invention relates to the novel modification A or A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



its use and pharmaceutical preparations comprising this crystal modification.

21 Claims, 2 Drawing Sheets

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4000 3500 3000 2500 2000 1750 1500 1250 1000 750
WAVENUMBER CM-1

FIG.1

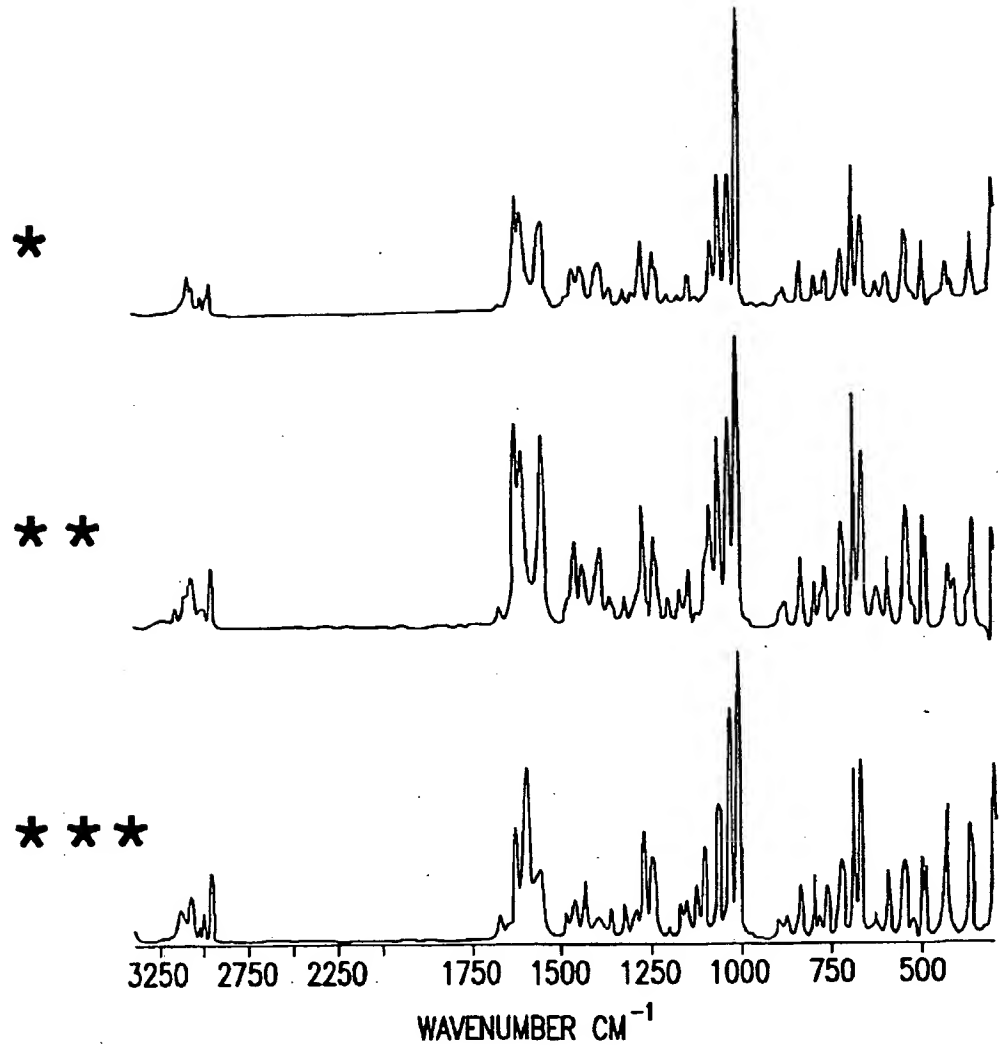
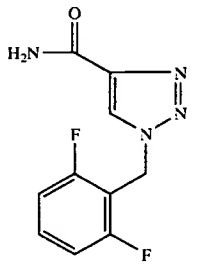


FIG.2

CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

BACKGROUND OF THE INVENTION

The compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



is described in the European Patent Application with the Publication No. 0 199 262 A2 (EP 199262), for example in Example 4. Valuable pharmacological properties are attributed to this compound; thus, it can be used, for example, as an antiepileptic. The compound 1-(2,6-difluorobenyl)-1H-1,2,3-triazole-4-carboxamide is obtained according to EP 199262, starting from 2,6-difluorobenzyl azide via the formation of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid, the procedure being analogous to Example 2.

EP 199262 provides no information at all about possible crystal modifications obtained. If the method according to the Example 4 is used in conjunction with Example 2, the crude 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide product obtained is finally crystallized from ethanol. However, EP 199262 gives no indication that such recrystallization is specifically to be applied, or on particular conditions that might be adopted. It has now surprisingly been found that the different crystal modifications (polymorphism) characterized below can be prepared by choice of specialty selected process conditions, for example through the choice of an appropriate solvent for the recrystallization or the duration of the recrystallization.

DESCRIPTION OF THE INVENTION

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be obtained in the novel crystal modifications A, A', B and C. These crystal modifications differ with respect to their thermodynamic stability, in their physical parameters, such as the absorption pattern of IR and Raman spectra, in X-ray structure investigations and in their preparation processes.

The invention relates to the novel crystal modifications A and A' preparation and use in pharmaceutical preparations comprising the crystal modifications.

The modification A', compared with A, has defects in the crystal lattice. These are detectable, for example, by X-ray analysis, e.g. by smaller line spacings with otherwise predominantly identical lines or bands.

The novel crystal modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide melts at 242° C. (239–245° C.).

In the FT infrared (FT-IR) spectrum (KBr pellet—transmission method), modification A or A' differs from

modifications B and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3412 cm^{-1} and 3092 cm^{-1} [cf. FIG. 1], which are not present in the Fr-IR spectra of the modifications B and C. In the range 4000–600 cm^{-1}, inter alia the following bands are obtained for modification A: 3412, 3189, 3092, 1634, 1560, 1473, 1397, 1325, 1300, 1284, 1235, 1125, 1053, 1036, 1014, 885, 840, 799, 781, 723, 688 and 640 cm^{-1}. For example, the apparatus IFS 88 (Bruker) can be used for the recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder—reflection method 180°), the modification A or A' differs from modifications B and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the band at 1080 cm^{-1} [cf. FIG. 2], which is not present in the Raman spectra of the modifications B and C. In the range 3400–300 cm^{-1}, inter alia the following bands are obtained for the modification A: 3093, 2972, 1628, 1614, 1558, 1465, 1446, 1393, 1279, 1245, 1147, 1080, 1061, 1036, 1014, 840, 724, 691, 667, 550, 499, 437 and 368 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for the recording of each of the FT Raman spectra.

The novel modification A has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.15 Å, 3.07 Å, 2.81 Å [cf. Table 1]. The measurement can be carried out, for example, in transmission geometry on an FR 552 Guinier camera from Enraf-Nonius, Deft (The Netherlands), using copper $K\alpha_1$ radiation (wavelength λ=1.54060 Å). The patterns recorded on X-ray film were measured using an LS-18 line scanner from Johannsson, Täby (Sweden) and evaluated using the Scanpi software (P. E. Werner, University of Stockholm).

Characteristic for the novel modification A is the thermogram in differential scanning calorimetry. It has an endothermic peak in the range from 230° C. to 260° C. The peak temperature is 239–245° C., and the endothermic signal is 209 J/g+/–10 J/g. The measurement was carried out on a Perkin Elmer DSC 7 in a closed pan with a heating rate of 20 K/minute. The typical sample quantity is about 4 mg. As a typical distinguishing feature compared with the modifications B and C, the thermogram of the modification A has no further thermal signal.

Crystals of the modfication A' have the same crystal structure as modification A. They differ from the modification A in the X-ray powder pattern in that they have slightly smaller line spacings between specific pairs of lines. These are the pairs of lines with the following interplanar spacings: 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å, 3.19 Å and 3.15 Å.

In the FT-IR spectrum (KBr pellet—transmission method), the modification B differs from the modification A or A' and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic is a band at 1678 cm^{-1} [cf. FIG. 1], which is not to be observed in the corresponding spectra of the modifications A and C. In the range 4000–600 cm^{-1}, inter alia the following bands are obtained for the modification B: 3404, 3199, 3125, 1678, 1635, 1560, 1475, 1393, 1357, 1322, 1286, 1237, 1051, 1036, 1028, 889, 837, 800, 719, 667 and 645 cm^{-1}. For example, the apparatus IFS 85 (Bruker) can be used for recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder—reflection method 180°), the modification B differs from the modifications A or A' and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3166 cm^{-1} and 1086 cm^{-1} [cf. FIG. 2], which are

not present in the Raman spectra of the modifications A and C. In the range 3400–300 cm^{-1}, inter alia the following bands are obtained for the modification B: 3166, 3089, 2970, 1678, 1628, 1614, 1559, 1464, 1441, 1391, 1275, 1244, 1147, 1086, 1062, 1036, 1014, 839, 773, 724, 690, 668, 595, 549, 500, 493, 430 and 365 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for recording of each of the Fr Raman spectra.

The modification B has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 11.0 Å, 8.3 Å, 5.18 Å, 4.88 Å, 4.80 Å, 4.42 Å, 4.33 Å, 4.19 Å, 4.12 Å, 3.81 Å, 3.50 Å, 3.41 Å, 3.36 Å, 3.32 Å, 3.28 Å, 3.24 Å, 3.05 Å, 2.83 Å [cf. Table 1].

In the thermogram in differential scanning calorimetry, the modification B has, in addition to an endothermic signal in the range from 230° C. to 260° C. (peak temperature 239–245° C.), a weak thermal signal at 205° C. (180–220° C.) as a typical distinguishing feature compared with the modifications A or A' and C.

In the FT-IR spectrum (KBr pellet—transmission method), the modification C differs from the modifications A or A' and B predominantly in the shape and in the relative intensity of many bands. Particularly characteristic is a band at 3137 cm^{-1} [cf. FIG. **11**], which is not to be observed in the corresponding spectra of the modifications A and B.

In the range 4000–600 cm^{-1}, inter alia the following bands are obtained for the modification C: 3396, 3287, 3137, 1657, 1631, 1602, 1559, 1475, 1392, 1323, 1287, 1237, 1122, 1104, 1047, 1035, 1012, 876, 839, 797, 773, 729 and 653 cm^{-1}. For example, the apparatus IFS 85 (Bruker) can be used for recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder—reflection method 180°), the modification C differs from the modifications A or A' and B predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3137 cm^{-1} and 1602 cm^{-1} [cf. FIG. 2], which are not present in the Raman spectra of the modifications A and B. In the range 3400–300 cm^{-1}, inter alia the following bands are obtained for the modification C: 3137, 3080, 3012, 2971, 1673, 1629, 1602, 1561, 1436, 1271, 1248, 1105, 1065, 1035, 1013, 839, 800, 767, 726, 690, 672, 593, 549, 500, 492, 435 and 370 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for recording of each of the FT Raman spectra.

The modification C has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 9.0 Å, 4.73 Å, 4.65 Å, 3.75 Å, 3.54 Å, 3.42 Å, 325 Å [cf. Table 1]. In the thermogram in differential scanning calorimetry, the modification C has, in addition to an endothermic signal in the range of 230° C. to 260° C. (peak temperature 239–245° C.), a very broad, weak, exothermic signal in the region of 180° C. compared with the modifications A or A' and B.

TABLE 1

Characterization of the modifications A, B and C (X-ray powder patterns):

Modification A:		Modification B:		Modification C:	
d [Å]	Intensity	d [Å]	Intensity	d [Å]	Intensity
10.9	weak	11.0	medium	9.0	medium
10.5	medium	8.3	medium	7.0	weak
6.6	weak	8.1	very weak	5.49	weak
5.63	weak	5.68	very weak	5.11	very weak
5.25	weak	5.18	very strong	4.80	weak

TABLE 1-continued

Characterization of the modifications A, B and C (X-ray powder patterns):

Modification A:		Modification B:		Modification C:	
d [Å]	Intensity	d [Å]	Intensity	d [Å]	Intensity
5.14	medium	5.11	weak	4.73	strong
4.94	weak	4.88	medium	4.65	very strong
4.84	very strong	4.80	strong	4.47	very weak
4.55	strong	4.71	very weak	4.19	very weak
4.42	very weak	4.61	weak	4.11	very weak
4.34	medium	4.45	weak	3.98	very weak
4.23	very weak	4.42	strong	3.83	very weak
4.16	weak	4.33	very strong	3.75	strong
4.07	medium	4.19	medium	3.73	weak
4.01	weak	4.12	strong	3.54	medium
3.68	very weak	4.09	weak	3.50	weak
3.64	very weak	3.99	very weak	3.42	strong
3.60	weak	3.95	very weak	3.25	medium
3.56	weak	3.84	weak	2.88	very weak
3.51	medium	3.81	medium	2.80	very weak
3.48	medium	3.65	weak	2.74	very weak
3.38	very weak	3.61	very weak	2.67	very weak
3.25	strong	3.58	very weak	2.64	weak
3.19	medium	3.54	weak		
3.15	medium	3.50	medium		
3.11	weak	3.47	very weak		
3.07	medium	3.41	medium		
2.93	very weak	3.36	very strong		
2.87	very weak	3.32	strong		
2.81	medium	3.28	medium		
2.76	weak	3.24	medium		
2.73	very weak	3.10	weak		
2.68	weak	3.07	weak		
2.62	very weak	3.05	medium		
2.53	weak	2.93	weak		
2.43	weak	2.88	weak		
2.40	very weak	2.87	very weak		
		2.83	medium		
		2.66	weak		
		2.63	very weak		
		2.55	weak		
		2.50	weak		
		2.46	weak		
		2.44	weak		
		2.37	weak		
		2.35	weak		

Single Crystal X-ray Analysis

Crystal quality and unit cell of modifications A, B, and C were verified by Weissenberg and precession photographs. The intensities were measured on a four-axis Nonius CAD-4 diffractometer. The structures were solved with the SHELXS-97 and refined with the SHELXL-97 software.

Modification A

Space group: $Pna2_1$—orthorhombic

Cell dimensions:

a = 24.756 (5)Å	b = 23.069 (4)Å	c = 5.386 (1)Å
v = 3075.9 $Å^3$	Z = 12	D_x = 1.543 gcm^{-3}
v per formula:	V_z = 256.3 $Å^3$	

9011 unique reflections; 2479 thereof significant with $I>2\sigma$ (I). 557 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 3.65% (wR_2 for all 9011 reflections: 11.34%).

Modification B

Space group: $P^{-}1$—triclinic
Cell dimensions:

a = 5.326(1) Å	b = 11.976(2) Å	c = 17.355(3) Å
α = 107.22(3)°	β = 92.17(3)°	γ = 102.11(3)°
v = 1027.9 Å^3	Z = 4	D_x = 1.539 gcm^{-3}
v per formula	V_z = 257.0 Å^3	

4934 unique reflections; 834 thereof significant with I>2σ (I). 232 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 4.20% (wR_2 for all 4934 reflections: 7.93%).

Modification C

Space group: $P2_1/C$—monoclinic
Cell dimensions:

a = 10.982(2) Å	b = 5.350(1) Å β = 91.59(1)°	c = 17.945(3) Å
v = 1053.9 Å^3	Z = 4	D_x = 1.501 gcm^{-3}
v per formula:	V_z = 263.5 Å^3	

3073 unique reflections; 1071 thereof significant with I>2σ (I). 187 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 5,02% (wR_2 for all 3073 reflections: 14.55%). Modifications A, A', B and C have valuable pharmacological properties; in particular, they can be used for the treatment of epilepsy.

The modification A or A' has significant advantages compared with the modification B and compared with the modification C. Thus, for example, comprehensive thermodynamic investigations such as thermomicroscopy, X-ray powder diffractometry, DSC, solubility tests and other experiments, have shown that the modification A or A' surprisingly has substantially better thermodynamic stability than the modifications B and C. Modification C, which can be obtained only under specific conditions, is the least stable of the three modifications. The crystals of the modification C are converted into modification B at as low as room temperature within a few weeks. The modification C is converted either into the modification A or A' or into the modification B, depending on experimental conditions.

It is particularly important for a drug that its pharmaceutical formulation ensures high and reproducible stability over a long period. These preconditions are fulfilled by incorporation of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the crystal modification A or A', owing to its high thermodynamic stability. In particular, this is displayed in a solid pharmaceutical dosage form.

A constant stability also permits reproducible bioavailability of an active ingredient. If an active ingredient is subjected to a conversion process, this may readily also cause the bioavailability to fluctuate, which is undesirable. Accordingly, pharmaceutical active ingredients or polymorphic forms thereof which are of primary interest for pharmaceutical developments are those which exhibit high stability and do not have the above-mentioned disadvantages. The crystal modification A or A' fulfills these preconditions.

Furthermore, the modification A or A' has, for example, a slower dissolution rate in water or in gastric fluid (so-called "slow-release effect"). This effect can be utilized primarily for long-term therapy where a slow or delayed release is desired.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by the following absorptions in the infrared spectrum (KBr pellet—transmission method): bands at 3092 cm^{-1} and 3412 cm^{-1}.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by characteristic lines with interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.07 Å and 2.81 Å, determined by means of an X-ray powder pattern.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by the characteristic lines with interplanar spacings (d values) as shown in Table 1.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by an endothermic peak in the range from 230° C. to 260° C., the peak temperature being 239–245° C. and the endothermic signal being 209 J/g+/–10 J/g.

Furthermore, the invention relates to the crystal modification A' which, compared with modification A, has defects in the crystal lattice.

The invention relates to the modification A' which, compared with modification A, has smaller line spacings between the pairs of lines with interplanar spacings 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å and 3.19 Å and 3.15 Å.

The invention relates to the essentially pure form of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide. The term "essentially pure form" means purity of >95%, in particular >98%, primarily >99%, based on the modification A or A'.

The invention relates to pharmaceutical preparations comprising the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide. The invention relates in particular to corresponding pharmaceutical preparations for the treatment of epilepsy and subindications thereof. The invention relates to the use of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide for the preparation of pharmaceutical preparations, in particular for the treatment of epilepsy and subindications thereof.

The novel modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be used, for example, in the form of pharmaceutical preparations which comprise a therapeutically effective amount of the active ingredient, if desired together with inorganic or organic, solid or liquid, pharmaceutically usable carriers, which are suitable for enteral, for example oral, or parenteral administration. Furthermore, the novel modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be used in the form of preparations which can be administered parenterally or of infusion solutions. The pharmaceutical preparations may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical preparations comprise from about 0.1% to 100%, in particular from about 1% to about 50%, of lyophilisates to about 100% of the active ingredient.

The invention also relates to the use of modification A or A' of 1-(2,6-difluorobeanzyl)-1H-1,2,3-triazole-4-

carboxamide as a drug, preferably in the form of pharmaceutical preparations. The dosage may depend on various factors, such as method of administration, species, age and/or individual condition. The doses to be administered daily are between about 0.25 and about 10 mg/kg in the case of oral administration, and preferably between about 20 mg and about 500 mg for warm-blooded species having a body weight of about 70 kg.

The preparation of modification A or A' is carried out, for example, as described in the embodiments below.

Preparation of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

EXAMPLE 1

A suspension of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate (about 62 parts by weight), methanol (475.2 parts by weight) and anhydrous ammonia (29.4 parts by weight) is stirred for about 24 hours at 50–55° C. in a closed vessel. The suspension is cooled to about 20° C. and stirred for about a further 2 hours. The product is isolated by filtration, washed with methanol (240 parts by weight) and dried at 40–60° C. in vacuo. Yield: 57.2 parts by weight= 98%. Modification A.

The starting compounds can be prepared, for example, as follows:

A mixture of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (167.1 parts by weight), methanol (552 parts by weight) and 96% sulfuric acid (35.7 parts by weight) is stirred for about 5 hours at 60–66° C. The suspension is cooled to about 20° C. and stirred for about a further 2 hours. The product is isolated by filtration and washed with methanol (198 parts by weight). A yield of about 160 parts by weight is obtained by drying at 40–60° C. in vacuo.

EXAMPLE 2

1 N sodium hydroxide solution (0.11 ml) is added to a mixture of 4-cyano-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole (2.20 g) and water (44 ml) at an external temperature of 95–100° C. while stirring. After 90 minutes, the suspension is cooled to 10° C. and the product is isolated by filtration, washed with water and dried at about 60° C. in vacuo. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is obtained in this manner, yield: 99.2% by weight, Modification A.

The starting material can be prepared, for example, as follows:

4-Cyano-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole

A mixture of 2,6-difluorobenzyl azide (34.2 g), 2-chloroacrylonitrile (17.73 g) and water (125 ml) is stirred for 24 hours at about 80° C. By increasing the external temperature to about 130° C., excess 2-chloroacrylonitrile is distilled off. The semisolid mixture is cooled to about 40° C., cyclohexane (50 ml) is added to the suspension and the mixture is brought to about 20° C. and stirred for about 2 hours. The product is isolated by filtration and washed with cyclohexane (75 ml) and then with water (50 ml). The moist product is mixed with water (100 ml), the suspension is filtered and the product is washed with water (50 ml) and dried at about 60° C. in vacuo. Yield: 38.04 g=86%.

Examples of the Recrystallization of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

EXAMPLE 3

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (75.0 g) is dissolved in formic acid (360 ml) at 50–55° C. by stirring. The solution is discharged in the course of 1 hour onto stirred methanol (375 ml) at about 20° C., a suspension-forming. After stirring has been continued for 2 hours at about 20° C., the product is isolated by filtration, washed with methanol (750 ml) and dried at about 60° C. in vacuo. Yield: 69.6 g=92.8%. Modification A.

EXAMPLE 4

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (22.86 kg) is dissolved in formic acid (111.6 kg) at 58–63° C. while stirring. The solution is discharged in the course of about 2 hours onto stirred methanol (131.9 l) at 20–25° C., after which washing with formic acid (7.6 kg) is carried out. A suspension forms. After stirring has been continued for at least 3 hours at about 20° C., the product is isolated by filtration and washed wit methanol (187.5 l). By drying in vacuo at about 60° C., the product is obtained as modification A in a yield of 93–94%.

EXAMPLE 5

1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (pure active ingredient, 4.0 g) is dissolved in 96% ethanol (500 ml, without denaturing agent) at about 80° C. while stirring. The solution is filtered into a suction bottle (1 liter) at about 20° C. (glass suction filter, pore size 10–20 μm), A suspension forming. After stifing has been continued for 5 minutes at about 20° C. and for 15 minutes at about 0° C., the product is isolated by filtration (about 0° to about 20° C.). The solvent-moist product (9.6 g) is investigated without subsequent drying. Modification A'.

FORMULATION EXAMPLE 1

Film-coated tablets each containing, for example, 100, 200 or 400 mg of modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with the following composition per dosage unit:

	mg	mg	mg
Core material			
Active ingredient	100.00	200.00	400.00
Anhydrous, colloidal silica	0.88	1.75	3.5
Microcrystalline cellulose	36.62	73.25	146.50
Hydroxypropylmethyl-cellulose	5.00	10.00	20.00
Lactose	20.00	40.00	80.00
Magnesium stearate	2.00	4.00	8.00
Maize starch	10.00	20.00	40.00
Sodium carboxymethyl-cellulose	5.00	10.00	20.00
Sodium laurylsulfate	0.50	1.00	2.00
Film coat			
Hydroxypropylmethyl-cellulose	3.22	6.43	12.87
Red iron oxide	0.04	0.09	0.18
Polyethylene glycol 8000, flakes	0.58	1.16	2.32
Talc	2.33	4.66	9.31
Titanium dioxide	0.83	1.66	3.32

The active ingredient is granulated with demineralized water. Milled lactose, maize starch, Avicel PH 102, cellulose-HP-M-603 and sodium laurylsulfate are added to the above mixture and granulated with demineralized water.

The moist material is dried and milled. After the addition of the remaining ingredients, the homogeneous mixture is

compressed to give tablet cores having the stated active ingredient content.

The tablet cores are coated with the film coat which is formed from the appropriate ingredients, the latter being dissolved or being suspended in water or in small amounts of ethanol with 5% of isopropanol.

DESCRIPTION OF THE FIGURES

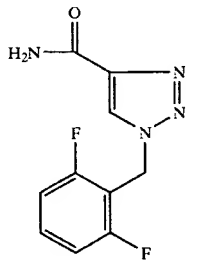
FIG. 1 shows the FT-IR spectra of the KBr pellets of modifications A, B and C.

FIG. 2 shows the FT-Raman spectra-of the powder of modification A, B and C.

In both Figures, the modification a is denoted by the symbol*, the modification b by the symbol** and the modification C by the symbol***.

What is claimed is:

1. Crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



characterized by characteristic lines at interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.15 Å, 3.07 Å, 2.81 Å, determined by means of an X-ray powder pattern.

2. The crystal modification according to claim 1, characterized by an X-ray powder pattern having the following characteristic lines at interplanar spacings (d values) of 10.9 Å (weak), 10.5 Å (medium), 6.6 Å (weak), 5.63 Å (weak), 5.25 Å (weak), 5.14 Å (medium), 4.94 Å (weak), 4.84 Å (very strong), 4.55 Å (strong), 4.42 Å (very weak), 4.34 Å (medium), 4.23 Å (very weak), 4.16 Å (weak), 4.07 Å (medium), 4.01 Å (weak), 3.68 Å (very weak), 3.64 Å (very weak), 3.60 Å (weak), 3.56 Å (weak), 3.51 Å (medium), 3.48 Å (medium), 3.38 Å (very weak), 3.25 Å (strong), 3.19 Å (medium), 3.15 Å (medium), 3.11 Å (weak), 3.07 Å (medium), 2.93 Å (very weak), 2.87 Å (very weak), 2.81 Å (medium), 2.76 Å (weak), 2.73 Å (very weak), 2.68 Å (weak), 2.62 Å (very weak), 2.53 Å (weak), 2.43 Å (weak), 2.40 Å (very weak).

3. The crystal modification according to claim 1, characterized by the following absorptions in the FT-IR spectrum (KBr pellet—transmission method) 3092 cm^{-1} and 3412 cm^{-1}.

4. The crystal modification according to claim 3, characterized by the following absorptions in the FT-IR spectrum (KBr pellet—transmission method): 3412, 3189, 3092, 1634, 1560, 1473, 1397, 1325, 1300, 1284, 1235, 1125, 1053, 1036, 1014, 885, 840, 799, 781, 723, 688 and 640 cm^{-1}.

5. The crystal modification according to claim 1, characterized by the following absorptions in the FT-Raman spectrum (powder—reflection method 180°): 3093, 2972, 1628, 1614, 1558, 1465, 1446, 1393, 1279, 1245, 1147, 1080, 1061, 1036, 1014, 840, 724, 691, 667, 550, 499, 437 and 368 cm^{-1}.

6. The crystal modification A according to claim 1, characterized by an endothermic peak in the range from 230° C. to 260° C., the peak temperature being 239–245° C., and the endothermic signal being 209 J/g+/−10 J/g.

7. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 1 but has defects in the crystal lattice.

8. The crystal modification A' according to claim 7, characterized by line spacings, smaller compared to modification A, between the pairs of lines at interplanar spacings 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å and 3.19 Å and 3.15 Å.

9. Modification A according to claim 1 in essentially pure form.

10. Crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide characterized by bands at 3412 cm^{-1} and 3092 cm^{-1} in the FT-IR spectrum.

11. Crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide characterized by bands at 1080 cm^{-1} in the FT-IR spectrum.

12. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 2 but has defects in the crystal lattice.

13. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 3 but has defects in the crystal lattice.

14. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 4 but has defects in the crystal lattice.

15. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 5 but has defects in the crystal lattice.

16. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 6 but has defects in the crystal lattice.

17. The crystal A' according to claim 7 in essentially pure form.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of crystal modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim 1.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim 7.

20. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 10 but has defects in the crystal lattice.

21. The crystal modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to claim 11 but has defects in the crystal lattice.

* * * * *

APPENDIX E

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 000000 | ISTMT | DATE PRINTED 12/12/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER NJ 07936-1080

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,740,669	**$930.00**	**$0.00**	**11/05/07**	**09/125,329**	**05/25/04**	**09/08/98**	**04**	**NO**	**4-30028/A/PC**

APPENDIX F

CONFIDENTIAL

Copy-1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

B-1

90-179

Food and Drug Administration
Rockville MD 20857

IND 35,534

Date SEP 28 1990
9/28/90

Pharmaceuticals Division-Ciba-Geigy Corporation
556 Morris Avenue
Summit, New Jersey 07901

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 35,534

Sponsor: Ciba-Geigy Corporation

Name of Drug: CGP 33101

Date of Submission: September 26, 1990

Date of Receipt: September 27, 1990

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

RECEIVED
OCT 05 1990
DRA FILE

FORM FDA 3228a (9/89) PREVIOUS EDITION IS OBSOLETE.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Ms. Susan DeCorte
Consumer Safety Officer
(301)443-3504

Sincerely yours,

John S. Purvis

John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-120 - yellow
HFD-120/CSO - green

IND ACKNOWLEDGEMENT

APPENDIX G

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
09/26/90	0000*	Original Submission
09/28/90		FDA LETTER (90-179) acknowledging receipt of our Original IND filed 9/26/90.
10/22/90	0001*	Serious Adverse Event (SAE)
12/06/90	0002*	SAE
01/03/91	0003*	Information Amendment Clinical
03/14/91	0004*	Pre-Clinical Study Report
03/25/91	0005*	Information Amendment Clinical
06/04/91		FDA LETTER: Clinical
09/17/91	0006*	Information Amendment Preclinical and clinical
09/18/91	0007*	Pre-Clinical Study Report
09/27/91	0008*	Annual Report
09/27/91	0009*	Pre-Clinical Study Report
10/11/91	0010*	SAE
10/23/91	0011*	SAE
11/04/91	0012*	Protocol Amendment
11/12/91	0013*	Information Amendment: preclinical safety
02/03/92	0014*	Information Amendment Clinical
02/06/92	0015*	Information Amendment Clinical, CMC
03/05/92	0016*	Information Amendment Clinical
05/21/92	0017*	Protocol Amendment
07/29/92	0018*	Information Amendment CMC
08/04/92	0019*	Pre-Clinical Study Report
09/08/92	0020*	Information Amendment Clinical
10/01/92	0021*	Pre-Clinical Study Report
10/26/92	0022*	Annual Report
10/30/92	0023*	Pre-Clinical Study Report
01/26/93	0024*	Pre-Clinical Study Report

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
01/28/93	0025*	Information Amendment Clinical
03/30/93	0026*	SAE
04/12/93	0027*	SAE
05/21/93	0028*	Pre-Clinical Study Report
07/20/93	0029*	Pre-Clinical Study Report
08/23/93	0030*	SAE
10/07/93	0031*	Pre-Clinical Study Report
10/15/93	0032*	Information Amendment Clinical
10/18/93	0033*	Annual Report
11/22/93	0034*	SAE
02/03/94	0035*	Pre-Clinical Study Report
03/11/94	0036*	SAE
03/16/94	0037*	SAE
05/05/94	0038*	SAE
05/05/94	0039*	SAE
05/12/94	0040*	SAE
06/16/94	0041*	SAE
06/24/94	0042*	SAE
07/13/94	0043*	SAE
07/22/94	0044*	SAE
08/24/94	0045*	SAE
08/25/94	0046*	Pre-Clinical Study Report
08/30/94	0047*	Information Amendment Clinical
10/10/94	0048*	Annual Report
10/26/94	0049*	SAE
11/03/94	0050*	SAE
11/23/94	0051*	SAE
02/17/95	0052*	SAE
03/02/95	0053*	SAE

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IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
03/09/95	0054*	SAE
04/07/95	0055*	Pre-Clinical Study Report
04/21/95	0056*	SAE
05/24/95	0057*	SAE
06/19/95	0058*	Pre-Clinical Study Report
07/07/95	0059*	SAE
07/31/95	0060*	Information Amendment Clinical
08/22/95	0061*	SAE
11/08/95	0062*	Annual Report
12/29/95	0063*	Preclinical Safety Report
02/28/96	0064*	Pre-Clinical Study Report
03/06/96	0065*	SAE
04/10/96	0066*	SAE
04/16/96	0067*	Pre-Clinical Study Report
04/17/96	0068*	Pre-Clinical Study Report
05/01/96	0069*	Information Amendment Clinical and CMC
05/01/96	0069*	Information Amendment Clinical and CMC
06/06/96	0070*	Pre-Clinical Study Report
06/07/96	0071*	Pre-Clinical Study Report
06/10/96	0072*	Pre-Clinical Study Report
07/31/96	0073*	Protocol Amendment
08/09/96	0074*	Pre-Clinical Study Report
08/19/96	0075*	Pre-Clinical Study Report
10/04/96	0076*	SAE
10/16/96	0077*	Protocol Amendment
10/21/96	0078*	Annual Report

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
10/21/96	0079*	SAE
11/26/96	0080*	SAE
12/09/96	0081*	Information Amendment Clinical
02/04/97	0082*	Information Amendment Clinical and CMC
02/12/97	0083*	General Correspondence Ciba Geigy: Transfer of IND to Novartis
02/12/97	0084*	General Correspondence Novartis accepts IND
03/03/97		FDA LETTER: acknowledges transfer of IND to Novartis
05/19/97	0085*	Information Amendment Clinical
05/19/97	0086*	Information Amendment Clinical
05/20/97	0087*	Pre-Clinical Study Report
05/20/97	0088*	Information Amendment Clinical
05/20/97	0088*	Information Amendment Clinical
05/20/97	0089*	Information Amendment Preclinical
05/23/97	0090*	Information Amendment Clinical and CMC
06/23/97	0091*	Protocol Amendment Clinical
07/24/97	0092*	Information Amendment Clinical
08/07/97	0093*	Information Amendment CMC
09/11/97	0094*	Information Amendment CMC
09/12/97	0095*	Protocol Amendment
09/19/97	0096*	Protocol Amendment
10/07/97	0097*	Protocol Amendment
11/14/97	0098*	Protocol Amendment
11/14/97	0099*	Protocol Amendment
11/14/97	0100*	Protocol Amendment
11/20/97	0101*	Information Amendment Clinical
12/17/97	0103*	Protocol Amendment

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IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
12/22/97	0102*	Protocol Amendment
12/22/97	0104*	Protocol Amendment
01/16/98	0105*	Protocol Amendment
01/16/98	0106*	Protocol Amendment
02/09/98	0107*	Protocol Amendment
02/09/98	0108*	Protocol Amendment
02/09/98	0109*	Protocol Amendment
02/09/98	0110*	Request for End-of Phase II Meeting
02/11/98	0111*	Annual Report
03/09/98	0112*	Protocol Amendment
03/09/98	0113*	Protocol Amendment
03/09/98	0114*	Protocol Amendment
03/30/98	0115*	Briefing Package for End-of-Phase II Meeting
04/10/98	0116*	Protocol Amendment
05/26/98	0117*	Protocol Amendment
06/17/98	0118*	Protocol Amendment
06/18/98		FDA LETTER: FDA minutes of the End-of Phase II meeting
07/01/98	0119*	Information Amendment CMC
07/17/98	0120*	Protocol Amendment
07/21/98	0121*	General Correspondence: Novartis minutes of the End-of Phase II meeting
07/29/98	0122*	General Correspondence: resent Novartis minutes of the End-of Phase II meeting
08/12/98		TELECON FROM THE FDA: CMC
09/02/98	0123*	Protocol Amendment
09/03/98	0124*	Protocol Amendment

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
09/09/98		FDA FAX: CMC
10/02/98	0125*	Protocol Amendment
12/02/98	0126*	Protocol Amendment
12/21/98	0127*	Protocol Amendment
12/22/98	0128*	Annual Report
01/26/99	0129*	Protocol Amendment
02/25/99	0130*	Information Amendment CMC
03/02/99	0131*	Protocol Amendment Clinical
03/03/99	0132*	SAE
03/05/99	0133*	Request for Pre-NDA Meeting
03/18/99	0134*	Protocol Amendment
03/25/99	0135*	Protocol Amendment
04/02/99	0136*	Information Amendment Clinical
04/12/99	0137*	Protocol Amendment Clinical
05/03/99		Telephone Report from Novartis: CMC
05/11/99		FDA LETTER: FDA minutes of the pre-NDA meeting.
05/26/99	0139*	Protocol Amendment
05/26/99	0140*	Request for Pre-NDA Meeting CMC
06/28/99	0141*	General Correspondence: Pre-NDA meeting CMC
06/29/99	0142*	Protocol Amendment
07/20/99	0143*	Briefing Package CMC
07/30/99	0145*	General Correspondence tradename
08/03/99	0146*	General Correspondence Clinical
08/11/99		FAX from FDA: FDA meeting minutes Pre-NDA meeting CMC
08/26/99	0147*	Protocol Amendment
08/31/99	0148*	Novartis Pre-NDA meeting minutes CMC
09/01/99		TELECON from FDA: CMC

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IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
09/08/99	0149*	Protocol Amendment
10/06/99	0150*	Protocol Amendment
10/26/99		FAX from FDA: trademark
11/15/99	0151*	Annual Report
12/06/99	0152*	Protocol Amendment
12/15/99	0153*	General correspondence: meeting minutes
03/02/00	0154*	Protocol Amendment
05/25/00	0155*	Protocol Amendment
06/21/00		FDA LETTER: Clinical
07/07/00	0156*	Protocol Amendment
08/08/00	0157*	Briefing Package: update
08/17/00	0158*	Information Amendment CMC
09/08/00	0159*	Protocol Amendment
10/03/00	0160*	SAE
10/26/00		FDA LETTER: CMC
08/24/01	0161*	Protocol Amendment
10/01/01	0162*	Annual Report
10/31/01	0163*	Protocol Amendment
11/19/01	0164*	Protocol Amendment
01/25/02	0165*	Annual Report
07/03/02		FDA LETTER: Clinical
01/07/03	0166*	Annual Report
04/02/03	0167*	Response to FDA Request: Clinical
08/13/03	0168*	Request for Meeting
08/29/03		TELECON from FDA in response to the August 13, 2003, request for a meeting.
10/07/03	0169*	Request for Meeting

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
10/15/03	0170*	Annual Report
11/19/03	0171*	Briefing Package
12/04/03		FAX to FDA: safety
12/04/03		TELECON from FDA with questions from the review of the Briefing Book
12/10/03		FAX from FDA containing a list of attendees
12/10/03		FDA LETTER: minutes of the December 10, 2003, pre-NDA meeting.
12/18/03	0172*	General Correspondence: orphan indication LGS
04/12/04		TELECONFERENCE WITH FDA
04/16/04	0173*	Protocol Amendment
05/18/04	0174*	Change of Sponsor Address
05/20/04	0175*	Change of Sponsor Address
07/29/04	0176*	Protocol Amendment
08/05/04	0177*	Protocol Amendment
08/25/04	NA*	Orphan Drug Application
10/04/04		Teleconference with FDA
10/06/04	0178*	Request for Meeting
10/21/04		TELECONFERENCE WITH FDA
10/21/04	0179*	Protocol Amendment
10/25/04		TELECONFERENCE WITH FDA
11/15/04	0180*	Protocol Amendment
11/15/04	0181*	Briefing Package
11/23/04		TELECONFERENCE WITH FDA
11/23/04	0182*	General Correspondence: Clinical
12/02/04	0183*	Annual Report
01/19/05		Incoming Correspondence from FDA
01/19/05		Incoming Correspondence from FDA
01/21/05	0184*	Protocol Amendment
02/24/05		TELECONFERENCE WITH FDA

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
03/15/05	0185*	Protocol Amendment
03/17/05		TELECONFERENCE WITH FDA
03/18/05		Incoming Correspondence from FDA
03/18/05		TELECONFERENCE WITH FDA
03/23/05	0186*	General Correspondence: tradename
03/30/05	0187*	Protocol Amendment
04/04/05		TELECONFERENCE WITH FDA
04/22/05		TELECONFERENCE WITH FDA
04/29/05		TELECONFERENCE WITH FDA
04/29/05	0188*	Response to FDA Request: Clinical
05/05/05		TELECONFERENCE WITH FDA
06/13/05		TELECONFERENCE WITH FDA
06/14/05	0189*	General Correspondence: Clinical
07/12/05		Incoming Correspondence from FDA
07/14/05		Incoming Correspondence from FDA
08/19/05		TELECONFERENCE WITH FDA
09/14/05		TELECONFERENCE WITH FDA
10/03/05		Incoming Correspondence from FDA
11/23/05	0190*	Annual Report
12/16/05		TELECONFERENCE WITH FDA
01/06/06	0191*	Response to FDA Request: Clinical
01/19/06		TELECONFERENCE WITH FDA
01/26/06	0192*	Response to FDA Request: Clinical
02/06/06		TELECONFERENCE WITH FDA
04/20/06		TELECONFERENCE WITH FDA

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
05/03/06		Incoming Correspondence from FDA
06/15/06	0193*	Information Amendment: CMC
06/20/06	0194*	Protocol Amendment
09/22/06	0195*	Protocol Amendment
10/31/06	0196*	Protocol Amendment
11/02/06	0197*	Protocol Amendment
11/09/06	0198*	Annual Report
11/21/06	0199*	Protocol Amendment
12/20/06	0200*	Protocol Amendment
01/11/07	0201*	Protocol Amendment
01/30/07	0202*	Protocol Amendment
02/28/07		E-Mail
02/28/07	0203*	Information Amendment
03/29/07	0204*	Protocol Amendment
05/03/07	0205*	Protocol Amendment
05/04/07		Incoming FDA Correspondence
05/30/07	0206*	Protocol Amendment
06/28/07	0207*	Information Amendment: Clinical
07/26/07	0208*	Information Amendment: Clinical
08/13/07	0209*	SAE
08/22/07	0210*	SAE
08/30/07	0211*	Protocol Amendment
09/21/07	0212*	Protocol Amendment
10/01/07	0213*	SAE
10/19/07	0214*	Information Amendment: Clinical

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
10/22/07	0215*	SAE
10/26/07	0217*	Letter of Authorization
10/29/07	0216*	Annual Report
10/31/07	0218*	SAE
11/20/07	0219*	Protocol Amendment
11/27/07	0220*	SAE
11/30/07	0221*	Protocol Amendment
01/25/08	0222*	Protocol Amendment
01/29/08	0223*	SAE
02/20/08	0224*	SAE
03/10/08	0225*	SAE
03/21/08	0226*	Protocol Amendment
04/10/08	0227*	SAE
05/06/08	0228*	Protocol Amendment
06/17/08	0229*	Protocol Amendment
07/24/08	0230*	SAE
08/20/08	0231*	SAE
09/03/08	0232*	SAE
09/05/08	0233*	Protocol Amendment
09/11/08	0234*	SAE
09/24/08	0235*	SAE
10/02/08	0236*	SAE
10/17/08	0237*	SAE
10/24/08	0238*	SAE

APPENDIX G

IND 35,534 COMMUNICATIONS

DATE	SERIAL NUMBER	DESCRIPTION
11/07/08	0239*	SAE

* - Communication to FDA

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
09/14/05		Teleconference with FDA
09/22/05		Teleconference with FDA
09/30/05		Teleconference with FDA
10/03/05		FDA Correspondence
10/03/05		Teleconference with FDA
10/04/05		Teleconference with FDA
10/05/05		Teleconference with FDA
10/06/05		FDA Correspondence
10/24/05		Teleconference with FDA
10/25/05		Teleconference with FDA
10/25/05		Teleconference with FDA
10/25/05		Teleconference with FDA
10/27/05		Teleconference with FDA
10/28/05		Teleconference with FDA
10/31/05		Teleconference with FDA

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
11/02/05		Teleconference with FDA
11/03/05		Teleconference with FDA
11/07/05		Teleconference with FDA
11/08/05		Teleconference with FDA
11/17/05	0000*	Original Application
11/18/05		FDA Correspondence
12/05/05		FDA Correspondence
12/06/05		Teleconference with FDA
01/09/06		Teleconference with FDA
01/19/06		Teleconference with FDA
01/23/06		Teleconference with FDA
01/24/06		FDA Correspondence
02/02/06		Teleconference with FDA
02/06/06		FDA Correspondence

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
02/07/06		FDA Correspondence
03/06/06		Teleconference with FDA
03/09/06		FDA Correspondence
03/10/06		Teleconference with FDA
03/13/06	0001*	Periodic Adverse Event Report
03/17/06	0002*	Response to FDA Request
04/05/06		FDA Correspondence
04/11/06		Teleconference with FDA
04/28/06		FDA Correspondence
05/23/06	0003*	Response to FDA Request

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
05/24/06		Teleconference with FDA
06/06/06		FDA Correspondence
06/15/06		Teleconference with FDA
06/15/06	0004*	Amendment to a Pending Application
06/19/06		FDA Correspondence
06/23/06	0005*	Amendment to a Pending Application
06/26/06		Teleconference with FDA
07/20/06		FDA Correspondence
08/01/06		FDA Correspondence
08/16/06		Teleconference with FDA
08/17/06	0006*	Amendment to a Pending Application

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
08/22/06	0007*	Amendment to a Pending Application
08/24/06		FDA Correspondence
08/28/06		FDA Correspondence
08/28/06		FDA Correspondence
08/30/06		FDA Correspondence
09/01/06	0008*	Response to FDA Request
09/05/06		FDA Correspondence
09/06/06		FDA Correspondence
09/15/06		FDA Correspondence
09/20/06	0009*	General Correspondence
10/03/06		FDA Correspondence

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
10/26/06		Teleconference with FDA
11/14/06		FDA Correspondence
11/15/06	0010*	Request for Meeting
11/28/06	0011*	Meeting Briefing Package
12/07/06		Teleconference with FDA
12/08/06		FDA Correspondence
12/14/06		FDA Correspondence
12/18/06		FDA Correspondence
01/05/07		FDA Correspondence
02/07/07		FDA's Final Meeting Minutes
03/02/07		FDA Correspondence
03/02/07		FDA Correspondence
03/09/07		FDA Correspondence

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
03/09/07		FDA Correspondence
03/21/07		Teleconference with FDA
05/23/07		FDA Correspondence
05/30/07		FDA Correspondence
09/24/07	0012*	General Correspondence
10/26/07	0013*	General Correspondence
01/30/08	0014*	General Correspondence
02/20/08	0015*	General Correspondence
02/29/08	0000*	Amendment to a Pending Application
03/25/08		Amendment to a Pending Application
03/25/08		NDA Follow Up Information
03/25/08		FDA Request for Information

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
03/26/08		Amendment to a Pending Application
03/27/08		FDA Request for Information
03/28/08		Response to FDA Request for Information
03/28/08		Teleconference with FDA
04/01/08	0001*	Response to FDA Request
04/11/08	0002*	Request for Information
04/11/08		Follow-up to FDA Request for Information
04/28/08		FDA Request for Information
04/28/08		Response to FDA Request for Information
04/28/08		Response to FDA Request for Information

APPENDIX G

NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
04/30/08		FDA Confirmation of Receipt of Additional Information
05/02/08		FDA Confirmation of Receipt of Additional Information
05/02/08		Response to FDA Request for Information
05/02/08		Response to FDA Request for Information
05/06/08		FDA Confirmation of Receipt of Additional Information
05/06/08		Response to FDA Request for Information
05/08/08	0003*	Response to FDA Request for Information
05/27/08		Response to FDA Request for Information
06/18/08		Provided Information Concerning Special protocol Assessment

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NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
06/20/08		FDA Information Concerning Manufacturing Site Inspection
06/25/08		Teleconference with FDA
07/08/08		Teleconference with FDA
07/15/08		Teleconference with FDA
07/16/08		FDA Communication – Establish Action Date
07/16/08		FDA Request for Information
07/22/08	0004*	Request for Special Assessment
07/25/08	0005*	Response to FDA Request for Information
07/31/08		FDA Request for Information
08/01/08		FDA Information Concerning Manufacturing Site Inspection
08/01/08		Teleconference with FDA
08/05/08	0006	Response to FDA Request for Information
08/05/08		Response to FDA Request for Information
08/05/08		Response to FDA Request for Information

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NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
08/06/08		Response to FDA Request for Information
08/08/08		Eisai Request for Teleconference
08/11/08		Submission of Additional Information to Prepare for Teleconference
08/13/08		FDA Communication Concerning Trade Name
08/14/08		Memo to Record – FDA Confirms Receipt of Information Concerning Manufacturing Site Inspection
08/19/08	0007*	General Correspondence Concerning Trade Name
08/20/08	0008*	Response to FDA Request for Information
08/20/08		FDA Confirmation of Information Review
08/20/08		FDA Confirmation of Trade Name Review
08/20/08		Desk Copy of Trade Name Information Provided to FDA
08/20/08		Tradename Review for Rufinamide
08/25/08	0009*	Response to FDA Request for Information

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NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT NUMBER	DESCRIPTION
08/27/08		Response to FDA Request for Information
08/28/08	0010*	Response to FDA Request for Information
08/28/08		FDA Letter Concerning Planned Manufacturing Site Inspection
09/03/08		FDA Request for Additional Clinical Information
09/03/08		FDA Clarification Concerning Requested Clinical Information
09/04/08		FDA Comments Concerning Labeling
09/10/08	0011*	Response to FDA Request for Labeling Information
09/15/08	0012*	Response to FDA Request for Information
09/17/08		FDA Clarification of Requested Clinical Information

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NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
09/19/08		Submission of FDA Requested Clinical Information
09/19/08		Update to FDA Concerning Revised Package Insert
09/22/08	0013*	Response to FDA Request for Information
09/25/08	0014*	Response to FDA Request for Information
10/03/08		FDA Letter Concerning Special Protocol Assessment
10/03/08		Response to FDA Request for Information
10/03/08		FDA Response to Special Protocol Assessment Information Concerning FDA Labeling Review
10/03/08		FDA Comments Concerning Draft Package Insert

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NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
10/03/08		Teleconference with FDA
10/03/08		Submission of FDA Requested Information
10/03/08		FDA Confirms Trade Name
10/08/08		FDA Update Information Concerning NDA Review
10/10/08	0015*	Response to FDA Request for Information Submission of Draft Package Insert
10/16/08	0016*	Response to FDA Request for Information
10/17/08	0017*	Response to FDA Request for Information

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NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
10/23/08	0018*	Response to FDA Request for Labeling Information
10/29/08		Rufinamide Med. Guide
10/29/08		Untitled
11/03/08	0019*	Response to FDA Request for Labeling Information
11/06/08		Submitted Minutes of the 11/05/08 Teleconference Submitted Revised Draft Package Insert
11/07/08	0020*	Request FDA Clarification Concerning Labeling Comments

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NDA 21-911 COMMUNICATIONS

DATE	DOCUMENT_NUMBER	DESCRIPTION
11/10/08	0021*	Response to FDA Request for Additional Information
11/14/08		NDA APPROVAL LETTER

* - Correspondence to FDA